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Those wishing to do so may remove the page and replace with it the original cover of the January–February issue.

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Commemorative Issue in Honor of Dr. Sadao Otani

JACOB CHURG, M.D. AND LOTTE STRAUSS, M.D.

GUEST EDITORS

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Sadao Otani, M.D.
1892–1969

Foreword

HANS POPPER, M.D., PH.D.

The tradition of an academic institution is based on the particular and frequently unique characters of the men who make up its community of scholars. Long before it became a medical school Mount Sinai was, besides being a hospital, an academic institution dedicated to teaching and research. The unusual aura of The Mount Sinai Hospital was based on this uniqueness of men and one of them was Sadao Otani, to whom this issue is dedicated.

Coming from a totally different culture, Dr. Otani imprinted his own character on the Department of Pathology, on the hospital, and especially on the many students who passed through the laboratory where he taught for 42 years. His unusual qualities were many, such as personal modesty, strength of unshakable conviction, and devotion to work coupled with a photographic memory—all of which resulted in great feats of diagnosis. Special emphasis has to be placed on his meticulous attention to details, a quality we so admire in Japanese scrolls. With these special qualities he combined the thoroughness of investigation developed, no doubt, during his German years as a young physician, and influenced by his long contact with Paul Klemperer, whose inductive thinking based on strong inference left a mark on the reasoning of Otani. His basic attention to details was strengthened by three attributes: high intelligence, a basic kindness, and a subtle sense of humor. His healthy aversion to nonsense was a useful antidote to much of the impatient, overzealous thinking in the hospital and in the school. Tribute is paid to the life of Otani and his considerable scientific achievements in the following pages. Here stress should be laid on his role in pathology as such, in the Department of Pathology of The Mount Sinai Hospital, and in the hospital community. His influence was not obvious to the casual observer because Otani, at least while I knew him, was a rather private person. He preferred to have the problems brought to him rather than to go out and attempt to be heard by those who did not seek him out.

During the many years of his work, American pathology underwent an extensive metamorphosis. In Otani's earlier years it was mainly based on the morphologic observations which had flourished in Central Europe and in England. Gradually, closer cooperation with clinicians, both physicians and surgeons, characterized pathology in this country, leading from the pathologic anatomy of Europe to the emphasis on the clinical pathologic correlations as reflected in the clinico-pathologic conferences which were developed in America. In his later years the thrust of American pathology moved to the general understanding of the disease processes rather than to the disease of the individual patient. Such a development entailed the danger of neglect of the morphologic observation. Otani, however, never wavered in the emphasis on the recognition of the morphologic picture as the basis of pathologic interpretation. He was willing to go along with clinical-pathologic correlation and was a master in development of the conferences, but his reliance on the morphologic picture to predict the outcome of a disease made him one of the giants of surgical pathology, a thoughtful consultant known and respected and sought out all over the nation.

His role in the Department of Pathology was similar. It was one of the fortunate acts of fate that he worked side by side with Klemperer, who represented in these years much of the advancing spirit of pathology in developing concepts. While the old master Klemperer would not deviate from the sound basis of observation, many of his young enthusiastic students would have been carried away in search of new concepts applying youthful imagination, had it not been for Otani, whose faithful clinging to demonstrable criteria insisted on "proof." Many of us were convinced that he maintained a viewpoint which might have been considered extremely conservative, but, again, reflected his aversion to nonsense. The large number of students in the Department of Pathology thus had the benefit of the dual influence, which most members of the department recognized and appreciated as guidance for their professional development.

In the transition of Mount Sinai from a research-oriented community hospital dedicated to excellence in training of physicians and in medical care, to a university hospital as the backbone of a new medical school, the quality and character of the medical staff was a key element. While Otani refrained from personally entering into the laborious and circuitous process of developing the school, he was a tower of strength, his advice was sought by many, his ability to judge people was uncanny, his insistence on excellence was a steady obstacle to expedience and compromise. Last but not least, his friendship, not lightly awarded, was a coveted treasure.

Otani was a blessing for American pathology, the Department of Pathology of The Mount Sinai Hospital, and the hospital's many patients who benefited from his tremendous experience. But the greatest blessing was the length of time in which he exerted his influence due to his unfailing loyalty to this institution.

Sadao Otani, 1892–1969: A Brief Memoir

JOSEPH C. EHRLICH, M.D.

> *. . . I on th' other side*
> *Us'd no ambition to commend my deeds,*
> *The deeds themselves, though mute, spoke*
> *loud the dooer.*
> Milton, *Samson Agonistes*

Dr. Sadao Otani was a man of few words. He spoke sparingly, wrote little, and published less. This verbal frugality was backed by a powerhouse of intellect, talent, and experience in a tiny (5 ft 2 in, 100 lbs) frame. His sprightly, shy figure was a commanding presence in The Mount Sinai Hospital and School of Medicine for 42 years—shining brightly even through the suffering and physical decline brought on during his last years by chronic and eventually fatal illness.

I rarely heard anyone address him by his first name, Sadao (Dr. Otani's own anglicization to avoid embarrassment to all who would find the Japanese name S'tuo difficult to pronounce.) To colleagues and friends, even intimates of a professional lifetime, he was "Dr. Otani," or occasionally, "Otani." The reason for this I do not know. Certainly in the forty years of my association with him (I first met him in 1929) I never addressed him in any way other than "Dr. Otani," partly, I believe, because I was unwilling to risk offending one for whom I held such high regard. No doubt many others felt the same.

When he died on March 7, 1969 at the age of 76, there passed from the scene one of the giants of The Mount Sinai Hospital and of surgical pathology. At this writing, two years later, his memory is vivid, unfaded; few days pass in the practice of my profession that I do not recall, and as often as not quote, from Dr. Otani's teachings some gem whose value has been established through the years and whose application helps to solve a problem at hand.

Dr. Otani was born on December 24th, 1892 in the small city of Kuwana-mie in central Japan near Nagoya. He was the youngest of six sons of a successful business man; there were also two daughters. He attended the second middle school of Mie prefecture and went on to medical school in Osaka. It was said that his decision to study medicine was influenced by his impression of the family physician's management of a serious illness of his mother.

Dr. Otani subsequently transferred out of Osaka to Chiba Medical College in Chiba-ken, a suburb of Tokyo; he graduated from there in 1918. While a student at Chiba, he collaborated with the Director of the Department of Pathology, Professor Tsutsui, in the latter's method for producing experimental coal tar cancer in the skin of mice. Decades later, Dr. Otani was to refer

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From the Departments of Pathology of the Bronx-Lebanon Hospital Center, Bronx, N. Y. 10457, and Albert Einstein College of Medicine, New York, N. Y. 10461.

critically to certain animal experiments from the standpoint of their relevance to human disease with the laconic comment "mice are not men." For two years following graduation, Dr. Otani remained in Chiba's Department of Pathology as assistant to Professor Ishibashi, who was appointed director following the death of Tsutsui.

Dr. Otani's next moves reflect the uncertainties and conflicts often endured at the crossroads in the search for professional fulfillment. He left Chiba's Department of Pathology suddenly to engage in the practice of obstetrics and gynecology in Kyoto. There was also a side trip to Korea to participate in emergency medical services for control of an epidemic of cholera. Finally, in 1923, he initiated steps to go to Germany for postgraduate training in anatomic pathology. It is likely that his contacts were made with the help of Dr. W. H. Schultze, Chief of the Section on Pathology at the Landeskrankenhaus in Braunschweig (Otani and Schultze had met in Tokyo while the latter's father was a Visiting Professor of Surgery at The University of Tokyo). It is furthermore probable that postgraduate study in Germany, hitherto financially inaccessible to Dr. Otani, became a practical possibility in 1923 because of the inflationary crisis in German currency.

It was in 1925, at the Postgraduate Hospital in New York City, that the historic meeting between Sadao Otani and Paul Klemperer took place. Klemperer, Pathologist to the Postgraduate Hospital and Associate Professor of Pathology at the now defunct New York Postgraduate Medical School, had arrived there in 1923 from Vienna via the Loyola Medical School in Chicago. The bond of personal loyalty and professional collaboration that was forged between them at the Postgraduate Hospital in 1925 was never broken. This bond was aptly described by Pollack as a "deep mutual respect and love which lay beneath a peculiar and characteristic outward mixture of bilateral diffidence, semiformality, humor, and solicitude" (1). Perhaps nothing emphasizes so impressively the depths reached by the collaboration of these two great figures as the fact that it became and remains a habit, almost a figure of speech, to link their names in discussing affairs relating to Mount Sinai's Department of Pathology. Even their obituaries, including this one, eulogize them as a pair, a fact noted by Professor Oota (2). During the years of their association, Dr. Otani declined offers from institutions in this country and Japan, motivated, at least in part, by his loyalty to Dr. Klemperer and dedication to Mount Sinai. At a farewell dinner at New York's Harmony Club in 1936 tendered by the staff of Mount Sinai Hospital on the occasion of Dr. Otani's return to Japan to join his wife and daughter, fears were expressed by speakers that Dr. Otani might be enticed to remain in Japan by his nostalgia for and love of his country, and by attractive offers of academic positions. In his response, Dr. Otani spoke movingly of his awareness of the staff's concern. He promised simply, and with deep emotion "I will come back". He did. He brought with him his wife and daughter Michiko; both had been delayed by the child's illness while on a visit to Japan.

When Klemperer was appointed Pathologist to The Mount Sinai Hospital in

1926, he took immediate steps to have Dr. Otani join him. To circumvent the obstacle of "no staff position available at present," arrangements were made for the temporary title "technician," at a starting annual salary of $1,300! This was soon corrected and Dr. Otani's subsequent staff positions rose from Assistant Pathologist, to Associate Pathologist, to Attending Pathologist and Associate Director of the Department of Pathology, and finally, in 1965, to Professor of Pathology at The Mount Sinai School of Medicine.

In December of 1930, a vivacious and charming schoolteacher, Miss Isako Makino arrived in New York City from Japan to visit her sister. Dr. Otani met Isako early in 1931 at the home of a mutual friend. The introduction was in formal Japanese style; they were married later that year. Three daughters were born of the union—Michiko, Hiroko, and Emy; there are two grandchildren—Robin and Paul.

Dr. Otani's dazzling performances in surgical pathology were deeply rooted in a lifelong study of human autopsies. Such tours de force as a diagnosis of leprosy on an isolated skin nodule in a native New Yorker after it had been misdiagnosed by dermatopathologists; the identification of a histologically atypical Hodgkin's disease in a tiny biopsy of a bone lesion thought to be primary; and the successful search for a primary lung carcinoma to explain what was thought to be a primary brain tumor are typical of the triumphs of his mastery of general autopsy pathology applied to the day-to-day problems of interpreting surgical specimens.

He was the taxonomist par excellence. Decisive structural features—the delicate fiber, the minute pigment granule, the "peculiar" cell formation, the mitoses nobody else could find—were often first perceived by Dr. Otani in problem slides and led him to a correct classification. A single cut with the straight razor he carried in the breast pocket of his white laboratory coat, through the right plane and at the right angle, sometimes established the diagnosis of a puzzling gross specimen. He seemed to have a mysterious "sixth sense," an unseen force, which guided his hand on a slide, like the planchette on a Ouija board, to bring into line with his microscope objective the one diagnostic field out of dozens of noncommittal fields in the section. He could do the same with a man. Professor Oota (2) recalls that during his travels he heard pathologists he visited refer to Dr. Otani's "golden eyes" or "hawk's eyes."

He had an extraordinary memory for his experiences with anatomical specimens. In its application to surgical pathology, it took the form of many, perhaps hundreds of vignettes of individual case experiences encapsulated in brief but precise recall of age, sex, history, gross, microscopic, and follow-up. This memory bank was open at all times for instant retrieval to bolster a diagnosis or back up a prognosis.

Dr. Otani was not one to foster his image. On the contrary, he was so modest and shy as to avoid notice and refuse honors, including the recent offer of a medal of honor by the government of Japan. His formidable reputation as a surgical pathologist was based upon one simple fact—follow-up of patients he had diagnosed proved him correct, not always, but so often that he attained that ultimate pinnacle of authority, the right to be wrong, sometimes. Less well known on the national and international stages than others who published and lectured more than he did, Dr. Otani was nonetheless the preferred consultant in surgical pathology to cognoscenti—a true pathologist's pathologist. Their faith in the accuracy of his diagnoses was based on proved performance matched by few and exceeded by none.

To Dr. Otani, photography was an indispensable tool of his craft. He once confided to me, quite seriously, that the secret of his memory for things anatomical was photography. He photographed all the specimens he wanted to remember and remembered all those he photographed. He did everything himself—the negative exposures, the developing, the printing, the labeling, the filing —the "works." He photographed during the days and evenings at the hospital; he photographed nights and weekends at home. He installed a box-like dark room, just high enough for him to work erect, in the corner of the dining area in his tiny apartment, where it still stands as it has for over 20 years, left untouched by his widow.

Many of his prints are more than mere photographs; rather they represent authoritative scientific documents painstakingly crafted by the skill, knowledge, and judgment of their creator. Each can be accepted as a standard or definition by which to judge new experiences. As an example, Dr. Otani's great photomicrograph of a bile canaliculus ruptured into a hepatic sinusoid, prepared by him for Dr. Klemperer's paper "Catarrhal Jaundice" (3) is reproduced in Figure 1. His montage of Letterer-Siwe disease (Fig. 2) in his paper "A Discussion on Eosinophilic Granuloma of Bone, Letterer-Siwe Disease and Schüller-Christian Disease" (4) displays the gross pathologic anatomy of a classic example of this rare disease and is characteristic of his authoritative style. It is not possible to trace all the papers and books published by staff members of The Mount Sinai Hospital with gross and microscopic illustrations by Dr. Otani. Major works, like Geist's "Ovarian Tumors" (5) depend in large part for their effectiveness on his photographic illustrations.

Dr. Otani was sensitive to artistic values in his photographs. Like the true professional, he paid meticulous attention to background, lighting, and arrangement. Once, when an intern proudly showed him a gross photograph he had taken of a pair of kidneys, Dr. Otani looked wryly at the arrangement with the lateral convex surfaces meeting in the center of the photograph and the hilar regions turned outward. Shaking his head in mild criticism he asked the intern, "What happened? Husband and wife have a fight?"

Dr. Otani's personal efforts in processing surgical material went much beyond photography. He was highly skilled in histologic techniques and not only supervised each step in the preparation by technicians of microscopic sections, but performed many of them himself, sometimes everything from cutting to special stains, when his goal was perfection for a special purpose such as an illustration for a lecture or publication. Daily routines followed such rigid patterns that they evolved into rituals, chief among which was the daily gross review by Dr. Otani of surgical material. Each afternoon, specimens received from the operat-

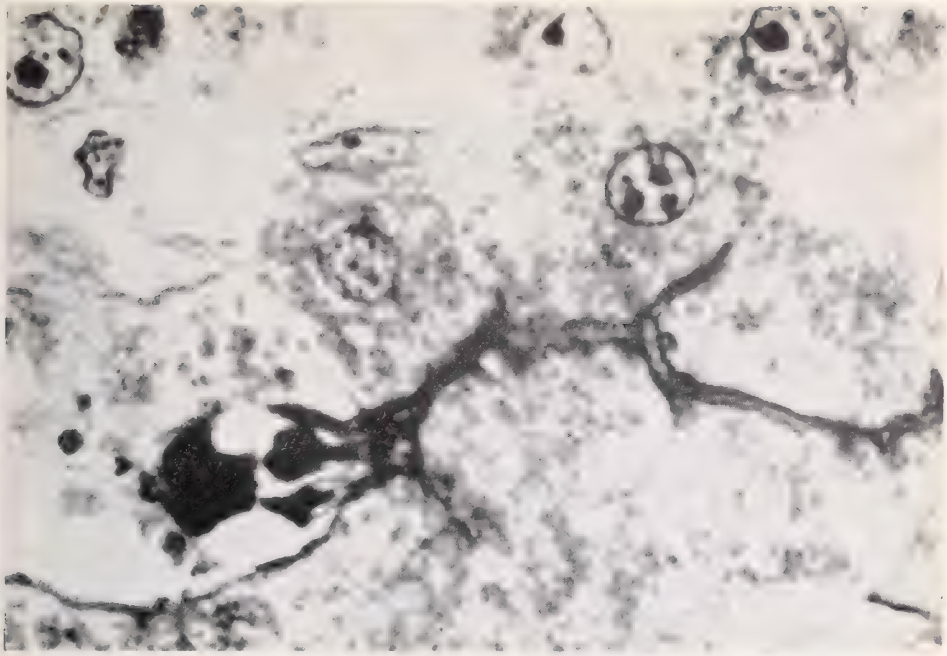

FIG. 1. Rupture of intracellular bile capillary with extravasation of bile; × 1,400. (Reproduced with permission from Arch Path 2:631, 1926.)

ing rooms were displayed on a table surrounded by interns, residents, fellows, and junior staff members. All eyes were riveted as Dr. Otani studied each tissue, asked and answered questions, and committed himself to a diagnosis. The lessons imparted in gross pathology were valued by those who served in the department as a memorable academic experience (Fig. 4).

At 9:00 P.M. each evening, for many years, Dr. Otani started the laborious manual transfers of tissue blocks, each in its individually labeled bottle, to chloroform and paraffin as demanded by the dehydration schedules followed in his laboratory during the nineteen thirties and forties. Finally, Dr. Otani reluctantly bowed to technical progress and permitted the installation of an Autotechnicon; he was surely one of the last, if not *the* last, to capitulate to automated tissue processing.

There were no hours. The laboratory lights burned through the evenings and often into the night, Monday through Saturday. One of Dr. Otani's students wrote his widow: "The fondest memories of my life are those evenings that I spent with [Dr. Otani] going over slides. . . . That was before you came; he had plenty of time. We would start about 7 P.M., work until eleven; then I'd go to the intern dining room for some huge 'bologny' sandwiches. After these were finished, we would start again and continue until one of us gave out at about 4 A.M. This went on for more than six months. It now seems to me that I never learned anything before or since. . . ." (7).

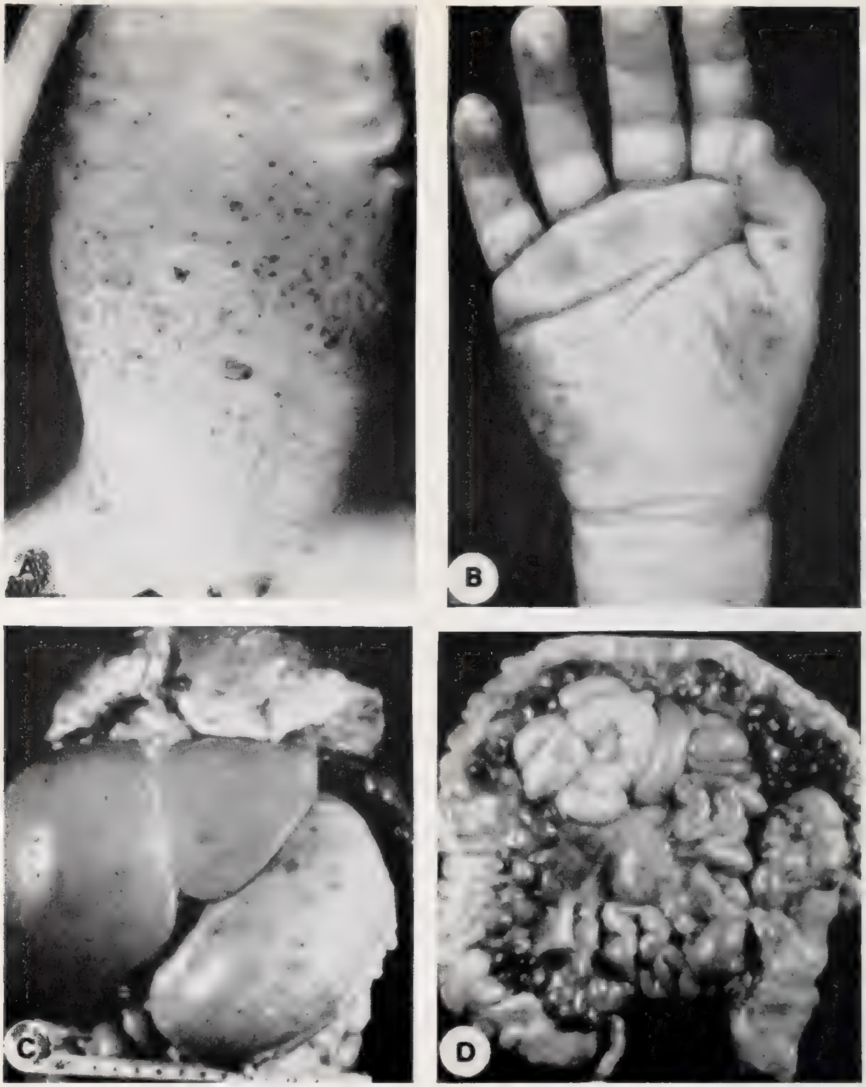

FIG. 2. Characteristic macroscopic lesions of Letterer-Siwe disease. Cutaneous hemorrhages (A and B). Marked hepatosplenomegaly. Distended stomach showing multiple hemorrhages (C). Diffuse enlargement of lymph nodes along the colon. Note hemorrhagic appearance of lymph nodes (D). Reproduced from J Mount Sinai Hosp 24:1079, 1957.

Dr. Otani's office on the first floor of the old Lewisohn Laboratory building survives as a graphic memory to colleagues and visitors. A tiny cubbyhole at one end of the residents' room, it was cluttered from floor to ceiling by papers, trays of slides, old microslide boxes filled with slides, homemade photomicrographic and projection equipment, books, notebooks, card files, and "Kodachrome" files. The only available workspace on the desk before the single chair was a tiny area containing his microscope (pre-World War II Zeiss with ordi-

FIG. 3. Otani and Klemperer at a review of gross autopsy specimens.

FIG. 4. Typical daily scene at Otani's review of gross surgical specimens.

nary achromats, Bitukni binocular attachment, and 10x eyepieces), homemade microscope lamp, and an ashtray filled with cigarette butts. To provide a place for a coffee cup and saucer, a board had been placed over a half-opened drawer; to set down a sheet of paper for writing, it was necessary, on the principle that two objects may not occupy the same place at the same time, to move something out of the way; this however usually created a new problem, namely where to move it. Once every year or two, Dr. Otani, with a sheepish grin of apology, would "straighten out" his room, a state of affairs that rarely lasted more than a few weeks. The apparent disorder of this room was deceptive; he could instantly retrieve a slide, photograph, or document when he wanted it.

This situation was somewhat (but not too much) improved when, in 1955, the laboratories were moved to the E floor in the new Atran Building. Here, in a slightly larger room, Dr. Otani presided over his desk and microscope for the

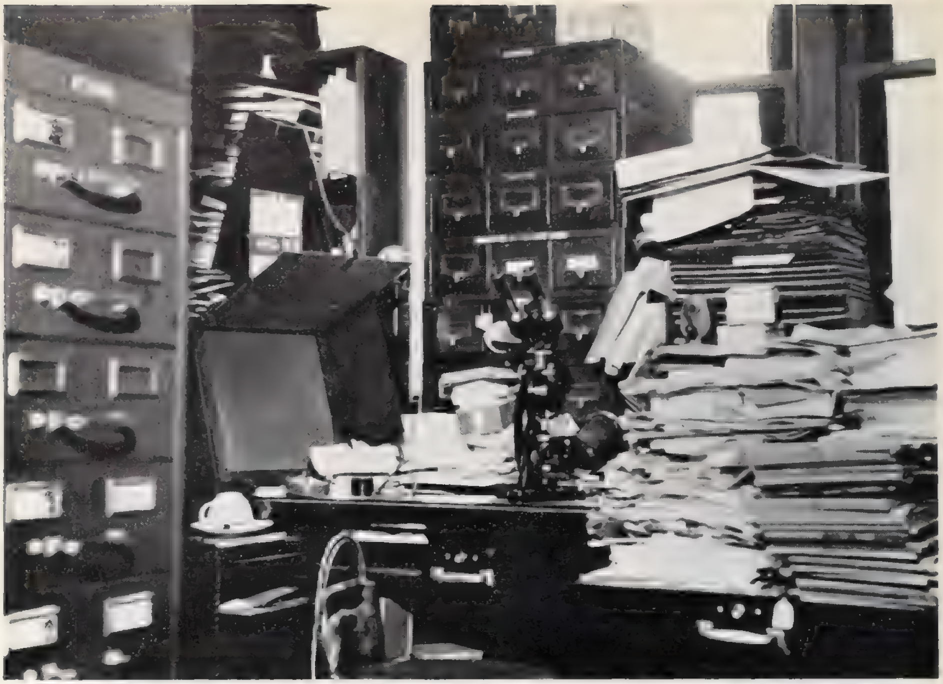

FIG. 5. Otani's desk in his office in the Lewisohn Laboratory.

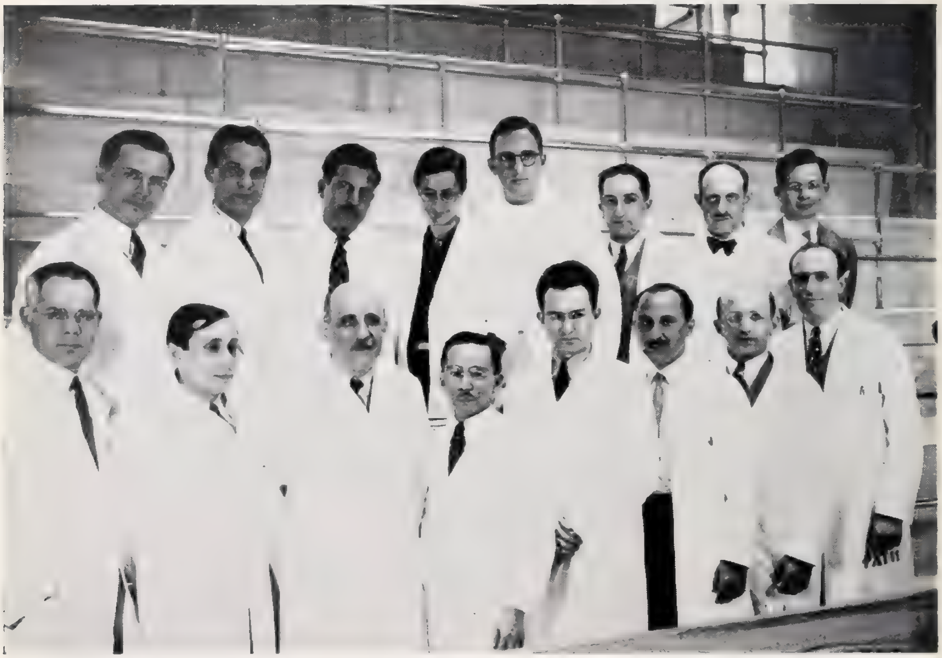

FIG. 6. The Pathologic Anatomy Staff poses in the autopsy room in the basement of the Lewisohn Building (Circa 1940). Front row (l. to r.) Abou Pollack, Vitale Kogan, Paul Klemperer, Sadao Otani, George Escher, Morris Steinberg, Julius Winer, Julian Jarman. Rear row (l. to r.) Leo Moss, Henry Horn, Arthur Allen, Alice Bernheim, Robert Landsman, Tobias Weinberg, Josef Gudeman, Arthur Ginzler.

rest of his life. Here, as in his old office, he taught his students, conferred with his staff, greeted his friends. And it was here, in numberless diagnostic sessions and consultations, that the benefits of his rare acumen were extended to the thousands of patients who never knew of his existence.

Dr. Otani's intellect was distinguished by its independence and originality. He learned from the masters, but much of what he knew was self-taught. He was not impressed by authority. Ideas had to withstand the withering fire of his criticism before acceptance. Once adopted, he was stubborn in his belief and resistant to change. His diffident manner concealed unusual strength of character; once committed he was almost immovable. The combination of intelligence, clarity of thought, critical attitude, and stubborn defense of his ideas produced in him a storehouse of classic concepts in pathologic anatomy that constituted a reference library for his students and made him a teacher of exceptional academic authority. In the jungle of lymphoma (a term he rarely used), for example, he was a trustworthy guide to splitting as opposed to lumping entities in that category. His clarification of the distinctions between eosinophilic granuloma of bone, Letterer-Siwe disease, and Schüller-Christian disease provided a base from which debate can safely take off, and affirmed original concepts which are receiving increasing general acceptance (6). His many and important contributions to the literature of pathologic anatomy are elaborated elsewhere in this issue; some were unfinished at his death and are herein published, with annotations by devoted colleagues, for the first time.

If this brief memoir seems as much hagiography as biography, it reflects the essence of the feelings shared by the many students, colleagues, and friends of Dr. Sadao Otani.

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Dr Otani's Teaching of Human Pathology: Its Principles and Methods

KEN MORI, M.D.

For more than forty years Dr. Sadao Otani taught human pathology at The Mount Sinai Hospital. His highly individual style of teaching, often expressed in simple and clear statements, has been of immeasurable benefit to his pupils, pathologists and clinicians alike. Although best known for his skill in surgical pathology he had vast experience in morbid anatomy as well. He was a meticulous prosector; and his careful dissection and examination of tissues at autopsy were the basis of his teachings and an inspiration to his students.

In addition to his published articles, and unpublished writings printed elsewhere in this issue of the Journal, he wrote short notes on various topics to the very last days of his life. These he carried in a thin briefcase, apparently with the intent of preparing them for publication as a supplement to his unfinished atlas-textbook. His publications number only ten (1–10), and he never read a paper at a major convention. His contributions, influence, and reputation rest mainly on his sharp analysis of individual cases, personal consultations, and his unique way of teaching. His short notes are far more characteristic of his approach than his more formal publications. Quotations from these often fragmentary notes written in the late 1960's and oral comments to his students form the source for the following presentation of his ideas. Photographs selected from his huge collection which dates back to the pre-Kodachrome era are memorable proofs of his unmatched photographic skill.

The following note on "Pancreatic Pseudocyst" typifies his approach and his style:

> "A fragment of pancreatic cyst wall was received for frozen section. Since it revealed myomatous tissue it was interpreted as a cystic myoma, and not a pancreatic cyst. The surgeon, however, insisted that the cyst had no connection with the stomach, and that it must have been of pancreatic origin. I then explained that there is no known case of cystic myoma of the pancreas. Nevertheless, I failed to convince the surgeon, and left the operating room. The next morning we received a cystic mass of grapefruit size, connected with a subtotally resected stomach. The surgeon expressed his apology for not having accepted the pathologist's opinion at first. After I had left the operating room he tried once more and found a connection between the cyst and the stomach posteriorly near the esophagus.
>
> One year later there was an almost identical case: A surgeon found a large pancreatic cyst at an exploratory operation, which he anastomosed to the stomach. The patient had to be reoperated a few weeks later, and I was consulted for the first time. At the second operation the tissue from the cyst

From the Department of Laboratories, Beth Israel Medical Center, New York, N. Y. 10003.

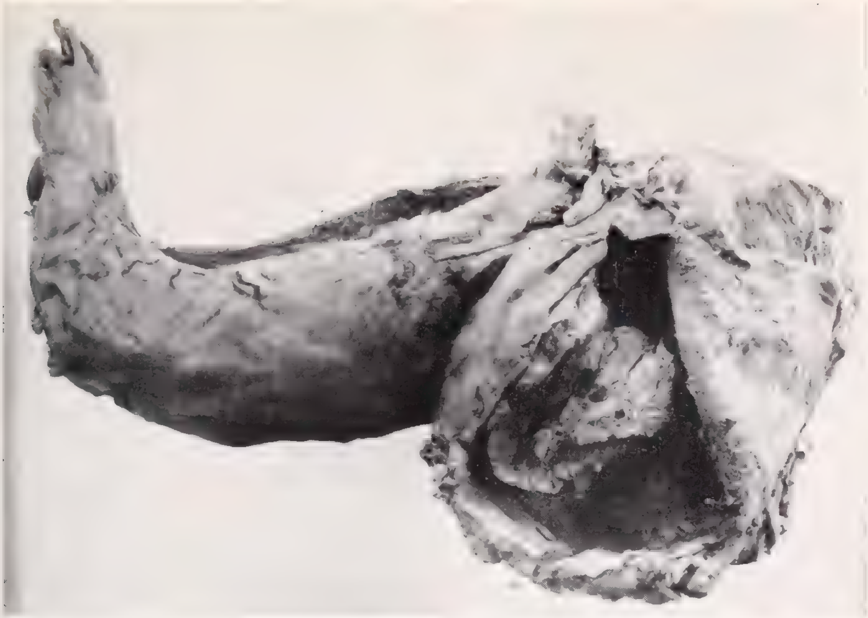

FIG. 1. Cystic exogastric leiomyoma of the stomach.

wall disclosed a myomatous structure which I interpreted as exogastric cystic myoma. Because of severe infection gastrectomy was not carried out.

Many textbooks describe inflammatory cysts or pseudocysts of the pancreas. However, pathologists rarely see such a cyst. Kaufmann in his *Textbook of Pathology* remarks that "some so-called pancreatic cysts are in reality not pancreatic cysts at all, but cysts of adjacent structures." Another textbook classifies a large dermoid cyst behind the pancreas as a pancreatic cyst which should be interpreted as a retroperitoneal cyst.

The existence of "inflammatory or pseudo-pancreatic cyst" is doubtful and, as Kaufmann suggests, most of these derive from adjacent structures. The only cyst truly originating from the pancreas may be a cystic fibroadenoma.

Whenever surgeons find a "pancreatic cyst", they should investigate its true identity and determine whether the cyst is connected with any adjacent organ."

He told his students of the above cases so often that they clearly remembered the name of the surgeon. Inclusion of the proper names of doctors, hospitals, and the particular circumstances surrounding a case was a salient feature of his case presentation and informal teaching. He believed that these seemingly redundant details were extremely helpful to illustrate a case, and in turn his views would be etched upon his students' memories. Confident of his power of observation and technical skill, he always selected his example out of specimens he had himself seen, palpated, photographed, sectioned, and probably stained, no matter how old the case may have been. He used the same case material year after year, even though he subsequently observed similar cases and undoubtedly stored these in his memory. He never changed his initial illustrative case unless his basic view underwent major modification. The two cases in the above-quoted note were at least fifteen years old, and his major reference was taken from Kaufmann's textbook published in the 1920's. To many minds accustomed to articles with a long list of up-to-date references, it is hardly believable that this note was written in 1968.

Another reason why he frequently adhered to a few selected old cases and to old reliable references, was his firm conviction that a conclusion drawn from a relatively small number of carefully studied cases is superior to that derived from a large number of case reports of mixed quality. He was not very much concerned with the number of his own cases or with statistical reports. This attitude is best shown in his published articles on gastrointestinal diseases, such as regional enterocolitis (9) and ulcerative colitis (8). It is generally accepted that regional enteritis was established as a disease entity in 1932 at The Mount Sinai Hospital where Drs. Otani and Klemperer performed the initial morphologic examination (11–13). Subsequently he must have seen at least 40 cases of various colitides per year, and if one adds the outside consultation cases, the

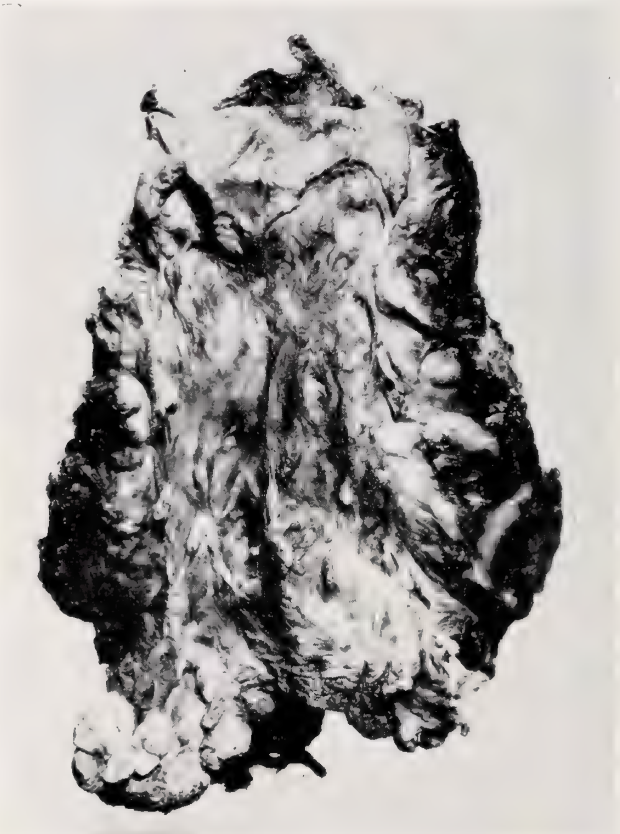

Fig. 2. Lymphogranuloma venereum in the ano-rectum.

total number could easily exceed 1800 cases during his professional life. He personally followed the great majority of these patients. Nevertheless, in his article he never cited the actual number of cases to indicate his vast experience at a single institution, even when he discussed the incidence of carcinoma in ulcerative colitis (8). Instead he stressed the need for careful evaluation of the entire specimen in order to exclude the fortuitous association between ulcerative colitis and carcinoma developing in an adenomatous polyp or in familial polyposis, or the development of colitis secondary to obstructive carcinoma (14, 15).

In 1955, when the concept of regional colitis was still controversial, Dr. Otani presented an objective approach to its morphologic diagnosis illustrated by a large number of photographs of gross specimens (9). His brilliant analysis of freshly resected intestinal specimens at his daily noon reviews, impressively illustrated his belief in gross observation as the primary diagnostic tool of the pathologist. Throughout the 1960's when the concept of regional colitis became generally accepted, possibly in haste (16), he maintained his unbiased attitude and cautioned against over-diagnosis. For instance, he pointed out that some of the so-called isolated rectosigmoid variants of colitis (17) may have been examples of lymphogranuloma.

To Dr. Otani, gross examination included not only inspection, but also palpation. He demonstrated that induration of a colonic polyp is the best index of malignancy on gross examination, and he convinced his surgical colleagues to make use of this observation at the operating table. During my residency I hardly ever saw a request for frozen section of an intestinal polyp. Subsequent histologic examinations showed that the surgical procedure based on palpation of polyps had been adequate.

Another example of his practical teaching concerned massive intestinal bleed-

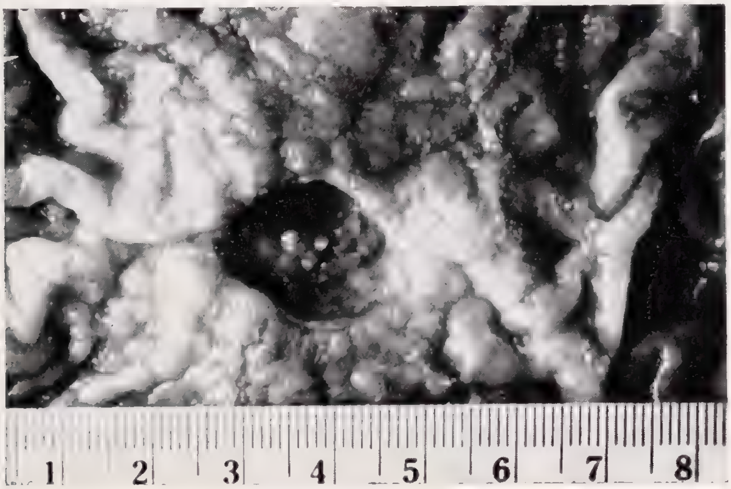

FIG. 3.

FIGS. 3–6. Gastric carcinoma originating in a chronic peptic ulcer. Symptoms of gastric ulcer for many years. (Fig. 4—shows a sharp interruption of the muscle layer on the right. Carcinoma shown in Figs. 5 and 6 is found on the left side of Fig. 4 where the muscle layer is obscured.)

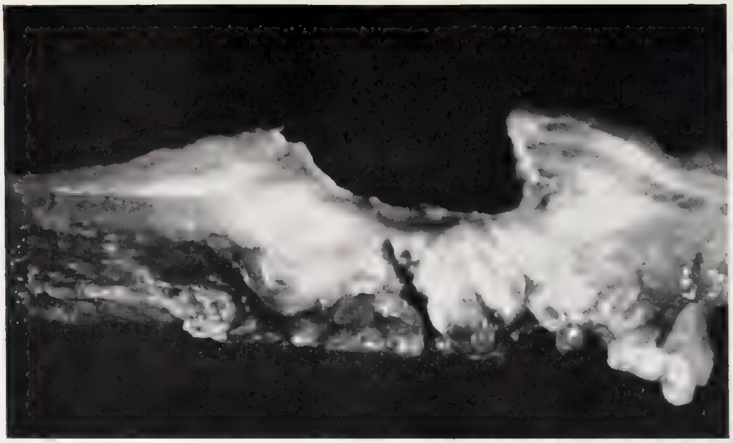

Fig. 4.

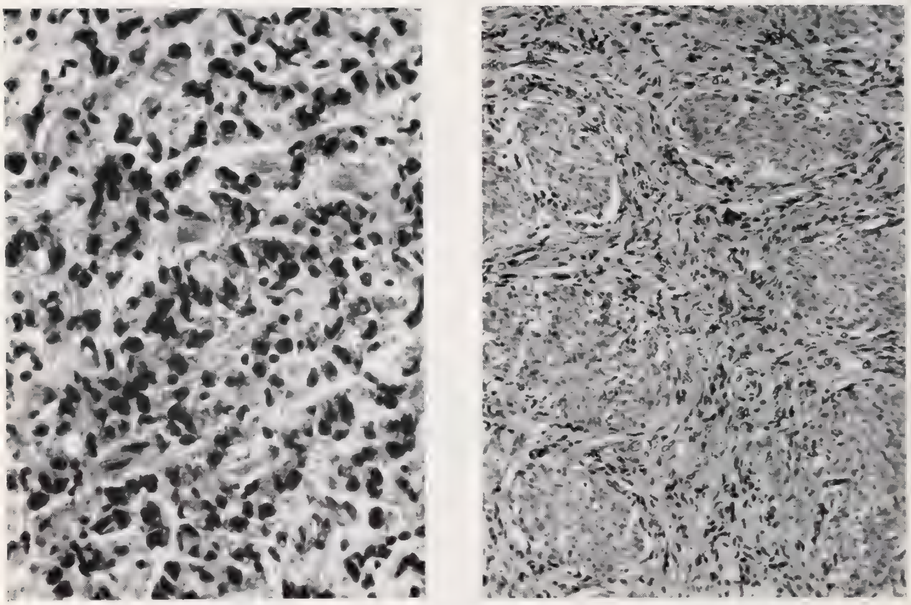

Fig. 5.

Fig. 6.

ing. Occasionally a resected segment of intestine filled with fresh blood fails to show the source of bleeding. In addition to the difficulty of locating an acutely inflamed diverticulum among other, secondarily blood-filled diverticulae, he called attention to the possibility of rapid transport of fresh blood from a lesion in an unresected proximal segment, such as an ulcerated leiomyoma. He also warned that bleeding temporarily stops during the immediate postoperative period, with the source of hemorrhage still remaining in the patient, and he cautioned against a false sense of security.

His way of examining gastric ulcers was unique: he pointed out the abrupt interruption of the muscle layer at the ulcer base as gross evidence of benign peptic ulceration, in contrast to diffuse muscular thickening and ill-defined obliteration of muscular markings in carcinomatous infiltration. Since this observation was not adequate for detecting a small focus of carcinoma at the ulcer edge (ulcer carcinoma), he carefully examined cross sections of many lymph-nodes for metastases, making a minimum of selected sections of the ulcer rather than indiscriminate serial sectioning of the entire ulcer. This selectivity was the basis of his whole approach to the histologic examination of specimens, which rested on his uncanny ability to recognize even slight abnormalities on gross examination. For this reason he personally sectioned tissues after they were fixed and before they were embedded in paraffin. This he did every morning for 30 years, until his declining health prompted him to delegate this task to his trusted associates. He considered this as a last opportunity to make a naked-eye observation of color, encapsulation, and other three-dimensional features of specimens before they were reduced to thin two-dimensional slides. He once confided that every day he committed himself to a single diagnosis for each case at the time of sectioning, as a means of self-education, and failure to confirm this microscopically was a most effective reminder that there was always room for improvement in the precision of his observation. Once he asked me for my diagnosis of what I thought to be a routine specimen of hemorrhoids, and finally pointed out a small nevus illustrating the histogenetic basis for the well-known, but uncommon, anal melanoma. More surprising for me, however, was his ensuing casual remark "it did not feel like a thrombosed varix yesterday," and I realized that he had already completed the differential diagnosis when he sectioned the specimen, and that this particular piece of hemorrhoidal tissue had been carefully selected by him to confirm his gross impression. This close correlation of visual and tactile observation on routine material enabled him to detect, with unbelievably high frequency, small uncommon lesions and unusual variations of seemingly banal alterations. Naturally, he was skeptical of statistical data reported from institutions where sectioning of tissues was routinely delegated to inexperienced junior staff.

Unfortunately, he never made known many of his keen observations. One could elicit these from him only if one discussed with him a specific case. To those who were not acquainted with his philosophy of self-reliance, his refusal to comment on general questions or engage in abstract discussions unrelated to specific experiences, may have appeared peculiar. At the monthly alumni meetings where unusual cases were informally presented to him by practicing former residents of the department, he matched each case with one of his own, and followed with concise comments. A large crowd usually attended these meetings, realizing the opportunity to learn from his invaluable experience. One remark —"in multiple polypoid tumors of the small intestine the possibility of metastatic melanoma must be considered"—appears elementary at first glance, since any malignant neoplasm may spread in this fashion. In practice however, awareness of this possibility led, in several instances, to a search for pigmentation, and the discovery of a forgotten excised "nevus." Anyone familiar with the unpredictable natural history and bizarre histology of melanoma will appreciate his terse remark crystallized from his enormous experience.

He often made a gross diagnosis of lymphoma in an intestinal specimen by noticing dilatation of the involved segment. This is caused by intraluminal pressure against a weakened wall, in contrast to carcinoma or chronic inflammation where progressive fibrotic reaction leads to stenosis. This observation was utilized by many radiologists who had worked with him, and found wide application in diagnostic radiology (18).

Dr. Otani's early publications include studies of the pancreas in meconium ileus and two morphologic investigations of the islets of Langerhans. His article entitled "Meconium Ileus with Congenital Stenosis of Main Pancreatic Duct" (5) is a little-known milestone in the history of cystic fibrosis of the pancreas, published at a time when the relation of meconium ileus to the generalized, genetic disorder had not yet been recognized, probably because the intestinal obstruction caused by the excessively inspissated meconium was then almost invariably fatal in the newborn. Successful surgical relief was not achieved until the early 1940's, and the survivors of such operations went on to develop the familiar clinical manifestations of "cystic fibrosis." Struck by the resemblance of the pancreatic changes in the infant with meconium ileus to those he had observed in older patients with obstructions of the pancreatic duct, or those following experimental obliteration of the duct in animals, Dr. Otani demonstrated stenosis of the main pancreatic duct by means of serial sections which he performed himself. Thus he provided a morphologic basis for the theory that the abnormal viscosity of the meconium is the result of pancreatic achylia. As biochemical, physiologic, and genetic insights in this disease expanded from the 1940's onward, interest in the abnormal pancreatic morphology was revived, and demonstration of pancreatic duct stenosis by serial sectioning of the pancreatic duct as well as by gross examination was no longer unusual (19). In 1962 stenosis of the pancreatic duct was demonstrated by an injection corrosion

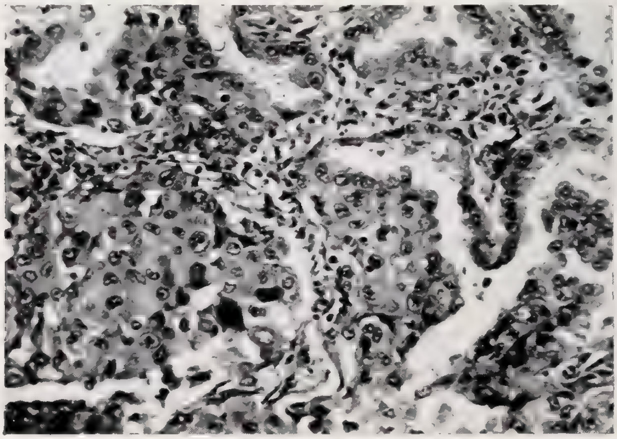

Fig. 7. Adenocarcinoma of the lung with neoplastic squamous metaplasia.

technique in two children with fibrocystic disease, one of whom had been a survivor of meconium ileus (20). The validity of Dr. Otani's approach has recently been borne out by various reconstruction methods revealing obstruction of the epididymis and vas deferens of adult males with cystic fibrosis, which demonstrated obstruction as the likely cause of male infertility in this disease (21). Dr. Otani first recognized a flower-like histologic pattern in the exocrine pancreas in patients with chronic congestive heart failure, before this was published by Van Glahn and Chobat in 1925 (22). This has more recently been referred to as "congestive pseudolobulation of the pancreas" (23), and though seldom mentioned in textbooks of pathology, is as distinctive as the congestive changes in the liver and spleen. He did publish his observations on the pancreas in two articles in 1927 (2, 3). Except for the paper on meconium ileus, he never went back to the subject of pancreatic pathology. He was very

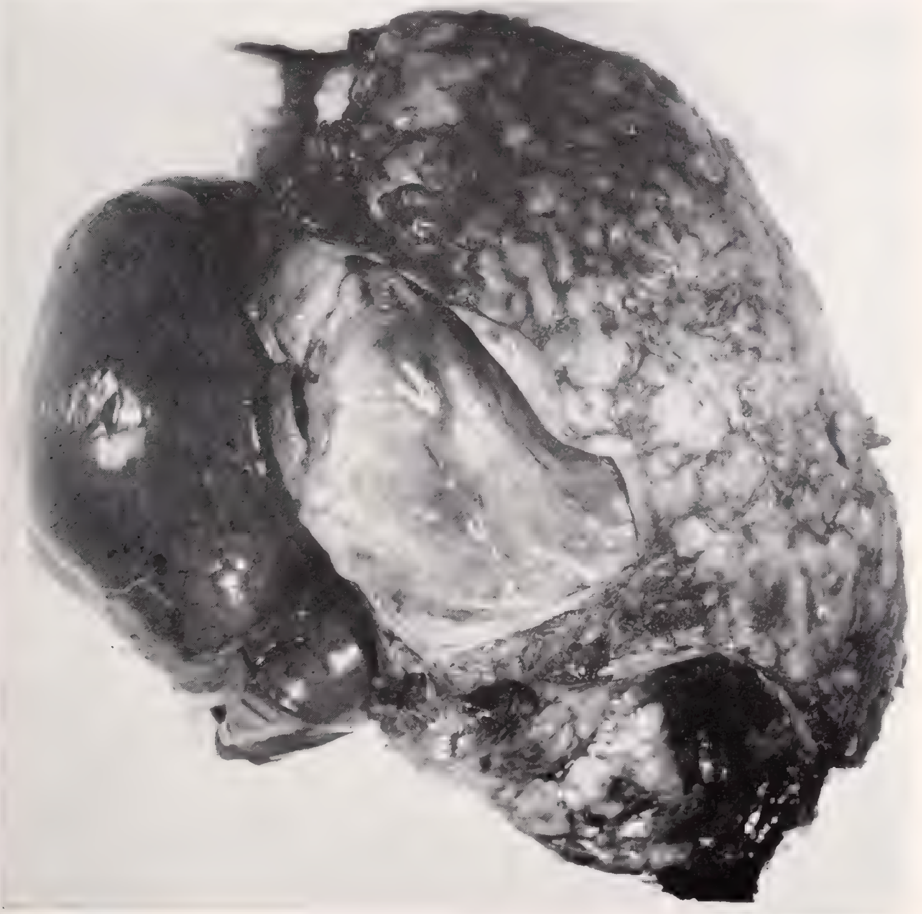

FIG. 8. Anterior view of the thoracic viscera showing diffuse growth of a mesothelioma of the left pleura.

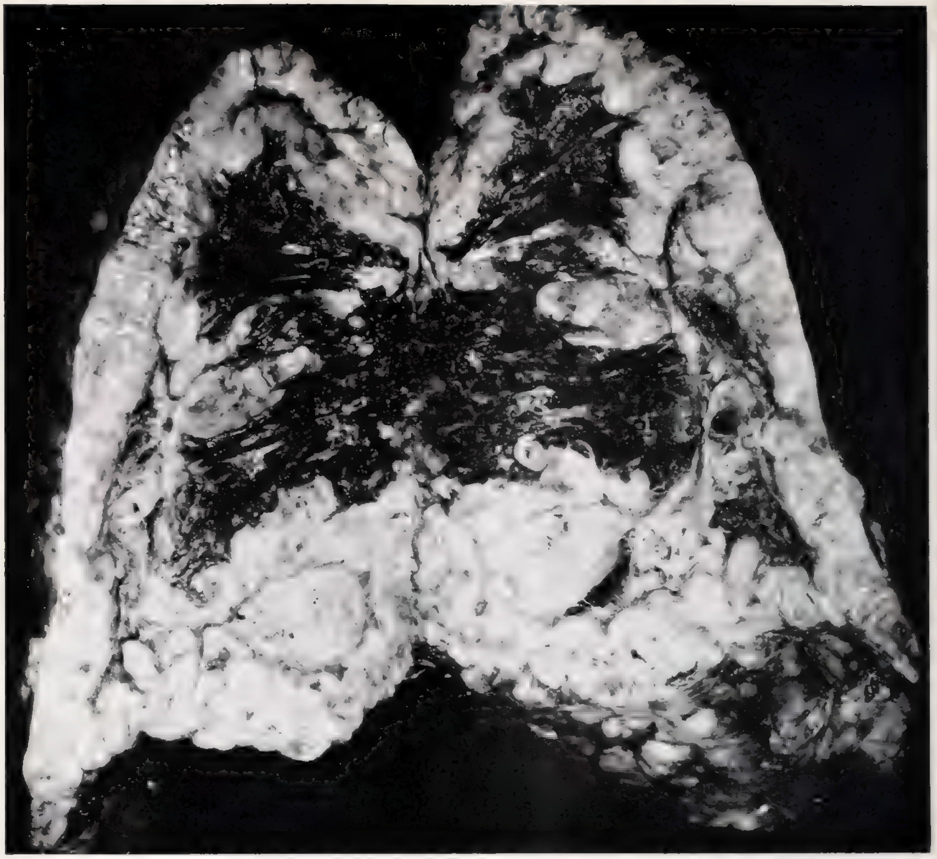

Fig. 9. Coronal section showing the complete encasement and infiltration of the lung by tumor (Fig. 8 of "Primary Neoplasm of the Pleura. A Report of Five Cases" by Drs. Klemperer and Rabin, Arch Path 11: 403, 1931. Reproduced from Dr. Otani's original print with permission of Arch Path).

much opposed to the indiscriminate proliferation of medical writing which often makes up for the lack of originality by long speculations and innumerable references. His ten publications cover a wide range of subjects in human pathology, each representing a fundamental contribution. In addition, the discoveries of the glomus jugulare tumor (24), and of bronchial adenoma (1932) (25) have been closely associated with his name. He well may be remembered as one of the great figures among pathologists.

Among his contributions to pulmonary pathology was the development of reliable criteria for the differentiation of primary from metastatic carcinoma. He taught that puckering of the serosal surface and anthracotic pigmentation within a peripheral tumor of the lung are features of primary carcinoma. The following passage is characteristic: "One of the primary lung carcinoma is adenocarcinoma developing in the periphery of the lung. It is always associated with existing fibrosis, and has been called 'scar carcinoma.' Because of its subpleural location, existing focal fibrosis produces puckering of the pleura overlying the tumor. Its cut surface reveals characteristic fibrotic areas and anthracotic pigment, while metastatic carcinoma shows no pigment. Microscopically, the lesion is adenocarcinoma, but it occasionally shows areas of squamous differentiation. In exceptional cases such tumors may show extensive squamous carcinoma and no obvious adenocarcinomatous areas. However, further sectioning of many blocks will reveal areas of adenocarcinoma. Therefore, if a tumor with the microscopic picture of squamous carcinoma is located at the periphery of the lung and has other characteristic features, I will not hesitate to make a diagnosis of adenocarcinoma."

Dr. Otani was convinced that squamous tissue never dedifferentiates into glandular structures. Therefore he classified histologically mixed types of carcinoma as adenocarcinoma regardless of the relative proportion of the two components.

On pulmonary adenomatosis he commented: "A peculiar lung condition known as adenomatosis was first observed among African sheep. In humans it is extremely rare. In advanced cases, especially those seen at autopsy, one finds markedly edematous pulmonary lobes, but no palpable masses or nodules. One gets the impression of lobar consolidation. Small groups of adenomatous foci are scattered throughout such a lobe. Since no solid areas are found, demonstration of adenomatous lesions on frozen section is rarely possible. Characteristically, no mitoses and no metastases are found. Histologically the lesion is benign. However, it is clinically malignant because the excessive mucus production suffocates the patient.

"Because of striking mucus production a certain number of pulmonary adenocarcinomas are erroneously interpreted as pulmonary adenomatoses. Such lesions exhibit solid areas which are caused by proliferation of fibrous stroma; in addition to the desmoplastic reaction, mitoses can be observed. This type of lesion is easily diagnosed by frozen section. Statements in the literature that fifty percent of cases of pulmonary adenomatosis show metastases seem to me erroneous."

His remarks document his cautious attitude toward the ante mortem differentiation of adenomatosis from adenocarcinoma, unless a desmoplastic reaction could be shown in the biopsy. He felt that so-called "pulmonary adenomatosis" often represents misinterpreted pulmonary metastases of well-differentiated mucus-producing adenocarcinoma arising elsewhere, especially in the pancreas.

The following note on bronchial adenoma illustrates his pioneering contribution to the recognition of this tumor: "Before 1928 bronchial adenoma was not recognized. In bronchial biopsies, any bronchial neoplasm was interpreted as carcinoma. However, some of these cases were considered benign on clinical grounds, especially by one of our outstanding diagnosticians, Dr. Harry Wessler; some of his patients, followed by him as long as five years after diagnosis, showed little progression of the lesion. About that time the incidental observation at autopsy, of a benign polypoid tumor projecting from the bronchial wall

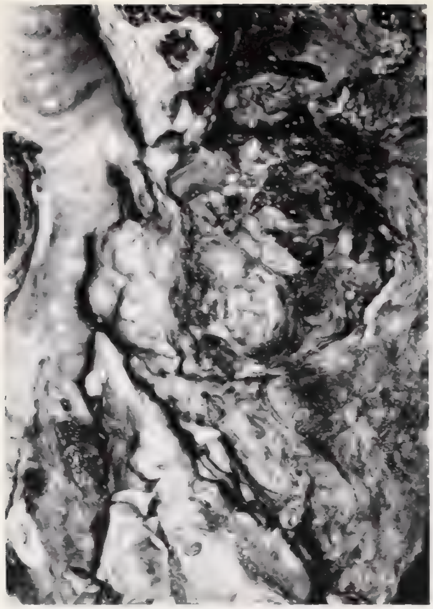

FIG. 10. Bronchial adenoma.

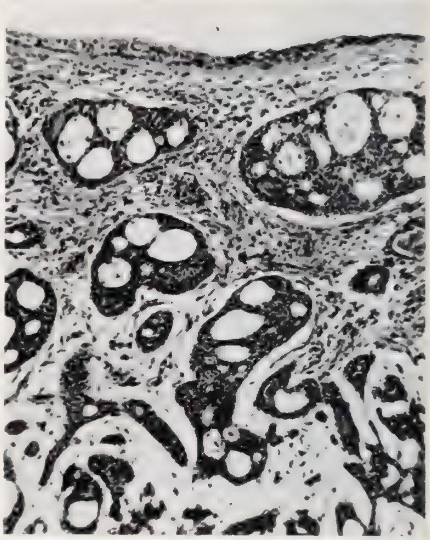

FIG. 11. Cylindroma of the bronchus.

led us to critically reexamine bronchial biopsies previously diagnosed as carcinoma, particularly from patients that Dr. Wessler had followed. This investigation led to the establishment of bronchial adenoma as a clinical and anatomic entity, first published by Wessler and Rabin (25). Subsequently, we studied many cases of bronchial adenoma; only a minority of these developed metastases to liver and bone. If one accepts the concept of 'metastasizing adenoma of the thyroid,' then metastasizing adenoma of the bronchus should be accepted. The great majority of bronchial adenomas are benign, and the patients are permanently cured if the tumor is completely resected".

Bronchial adenoma as defined by Dr. Otani would today be classified as carcinoid tumor of bronchus. This he recognized though he pointed out variable staining with silver stains of the bronchial tumor, and capricious secretion of serotonin. On the other hand, he separated cylindroma of bronchus as a mixed tumor similar to that seen in salivary glands. This view is expressed in a publication by Kramer and Som (26) and is currently held by others (27). The following is Dr. Otani's comment:

> "Cylindroma is a slow-growing malignant epithelial tumor with a honeycomb histologic pattern. Since it is a variant of mixed tumor, it is found wherever mixed tumors occur. For this reason the most common location is in the salivary glands. Various regions of the buccal cavity, including the soft palate, can be sites of this tumor. The trachea and bronchi are also known sites. I have observed a case of cylindroma of the breast in which a lung metastasis was removed ten years after the initial excision. Histologically neither cellular atypism nor mitoses was found. The malignant character was shown by direct invasion of lymphatics in the adjacent tissue.

This perhaps is the only histologic sign of its malignant behavior. Therefore a wide resection is essential to prevent recurrence. It does not metastasize in early stages. Many years later it may spread to the lung or liver through the blood stream.

A number of pathologists do not separate bronchial adenoma from bronchial cylindroma. This leads to confusion in definition and classification. Other pathologists have classified this tumor as adenocarcinoma. This is an over-simplification, disregarding the biologic characteristics of this tumor."

His classification of pulmonary neoplasms is unique:

"The classification of lung tumors in textbooks is often too complicated and confusing. It can be quite simple in my opinion. After examining very many lung tumors I am convinced that the following classification is useful:

A. *Primary Tumors*

1. *Common*

Malignant	Bronchial	squamous carcinoma
	Periphery of lung	adenocarcinoma
Benign	Bronchial	adenoma

2. *Rare but important*

Malignant	Bronchus and Trachea	cylindroma
	Central lung	bronchial adenocarcinoma
	Lobar involvement	adenomatosis
Benign	Chondroma (Hamartoma)	
	Lipoma	
	Neurofibroma	

B. *Metastatic Tumors*

Some cases are important: for example, a solitary nodular metastasis in the lung."

It is obvious that this classification does not include many histologic types found in other classifications. There are only two major types, namely, peripheral adenocarcinoma, and bronchial squamous carcinoma. All other histologic forms are assigned to one or the other category; for example, oat cell carcinoma is considered a poorly differentiated form of squamous carcinoma. The assignment was based less on histology than on gross appearance and location within the lung. This facilitated the assignment of histologically undifferentiated tumors.

The second major subdivision was by incidence, into "common" and "rare", and the list of rare neoplasms was deliberately kept short. The importance of solitary metastatic nodules was emphasized. If according to his criteria a tumor had the appearance of a metastasis, he, as well as his students, made great efforts to find a primary tumor elsewhere in the body, and were successful on many occasions. His classification was of great practical value and did not waste time on nonessential details and semantic hairsplitting.

His concern with metastatic lung tumors is reflected in his views on the relationship between smoking and lung cancer. Perhaps he was also influenced to some degree by his own life-long habit of cigarette smoking. However, he rightly maintained a skeptical attitude toward statistical evidence that was not based on careful autopsy studies.

Dr. Otani maintained a very high index of suspicion in the diagnosis of laryngeal biopsies. His experience had taught him to regard even moderate histologic and cytologic irregularities in the epithelium of the vocal cord as evidence of carcinoma, especially when dealing with verrucous growths. This was in contrast to his conservative approach to epithelial lesions of the uterine cervix.

He also wrote a short note on Schmincke's tumor:

> "There is a distinct type of carcinoma which occurs in the nasopharyngeal mucosa. It is a very immature type of carcinoma with the tumor cells having distinct nucleoli similar to those of seminoma. This histologic characteristic, and the marked radiosensitivity of this tumor warrant its interpretation as embryonal cell carcinoma. Since Schmincke's original publication various names have been given to this tumor, such as endothelioma, lymphoepithelioma, transitional cell carcinoma, even sarcoma. Some pathologists think the controversy is largely over names. However, I do believe that a correct terminology means proper understanding of this tumor, and therefore I prefer "embryonal cell carcinoma" which best indicates its biological character. If properly treated by radiation, the patient may greatly improve, and so-called five-year survival is well known, while transitional cell carcinoma which typically occurs in the urinary system is not radiosensitive. The term "lymphoepithelioma" is most confusing, because it implies that the lymphocytes seen in embryonal cell carcinoma are neoplastic, while in reality they are preexisting lymphocytes abundant in the region where this neoplasm arises. In biopsies of Schmincke's tumor I have always observed groups of embryonal cells within the subepithelial lymphatic tissue. Even the earliest tumor failed to show its mucosal origin. However, careful examination of such biopsies practically always shows ulceration. I believe that this is the source of confusion in biopsy interpretation and terminology, and in my opinion this tumor originates from the surface epithelium."

Although there is no publication by Dr. Otani on the glomus jugulare tumor of the ear, this tumor is often referred to as "Otani's tumor." A recent monograph by Dr. Rosenwasser, who also wrote the first article on glomus jugulare tumor (24), gives credit to Dr. Otani for first recognizing this entity which initiated widespread interest in neoplasms of the branchial glomera (28).

Dr. Otani was an early advocate of wide resection of benign mixed tumors of the salivary glands as opposed to simple enucleation (29). His influence in the recognition and therapy of certain lesions of the head and neck is evident also in the publications, by Kramer and Som on papilloma durum of the nasal cavities and on amyloid tumors of the larynx (30, 31).

The article "Malignant Nephrosclerosis (Fahr)" by Klemperer and Otani (6)

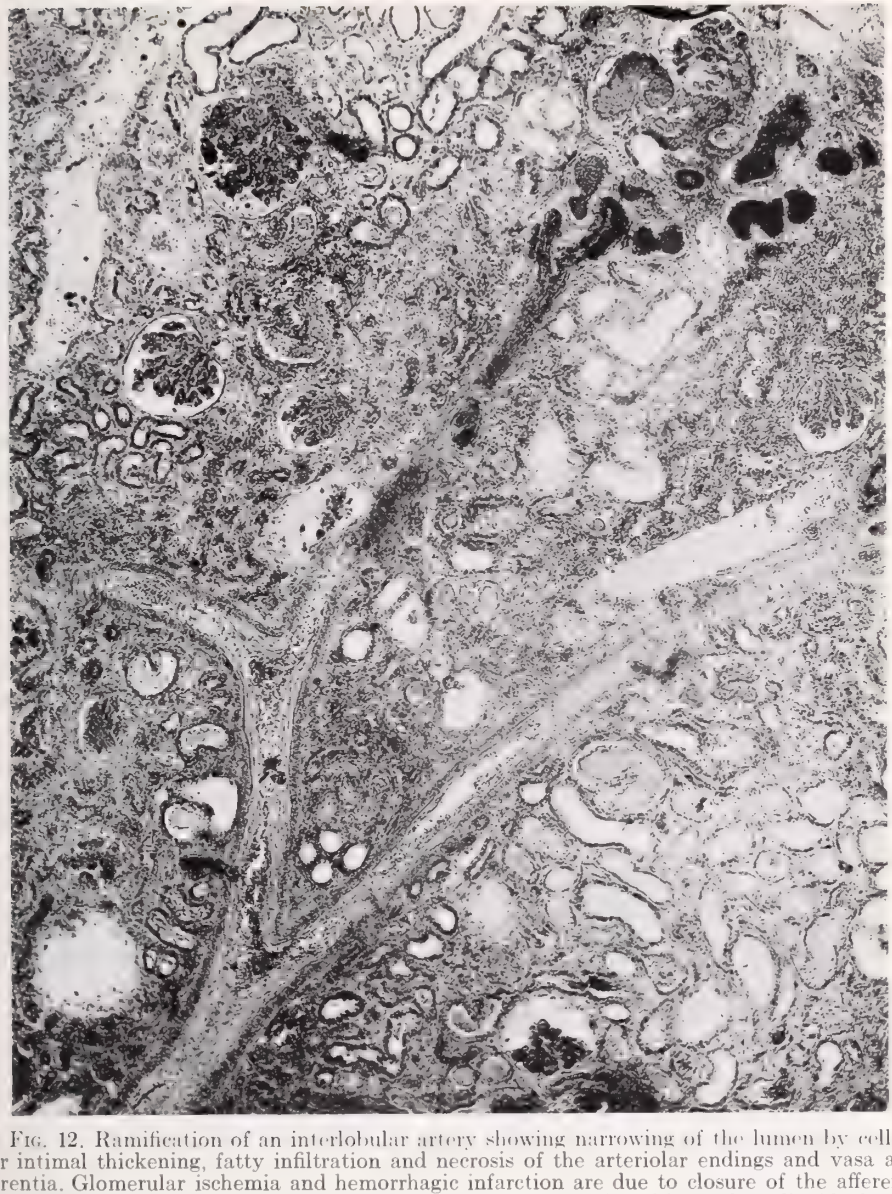

FIG. 12. Ramification of an interlobular artery showing narrowing of the lumen by cellular intimal thickening, fatty infiltration and necrosis of the arteriolar endings and vasa afferentia. Glomerular ischemia and hemorrhagic infarction are due to closure of the afferent arteriole. Sudan-hematoxylin stain. (Note: the tissue was sectioned by carbon-dioxide freezing method for Sudan stain. Fig. 20 in the paper on Malignant Nephrosclerosis. Reproduced from the original print with permission of Arch Path).

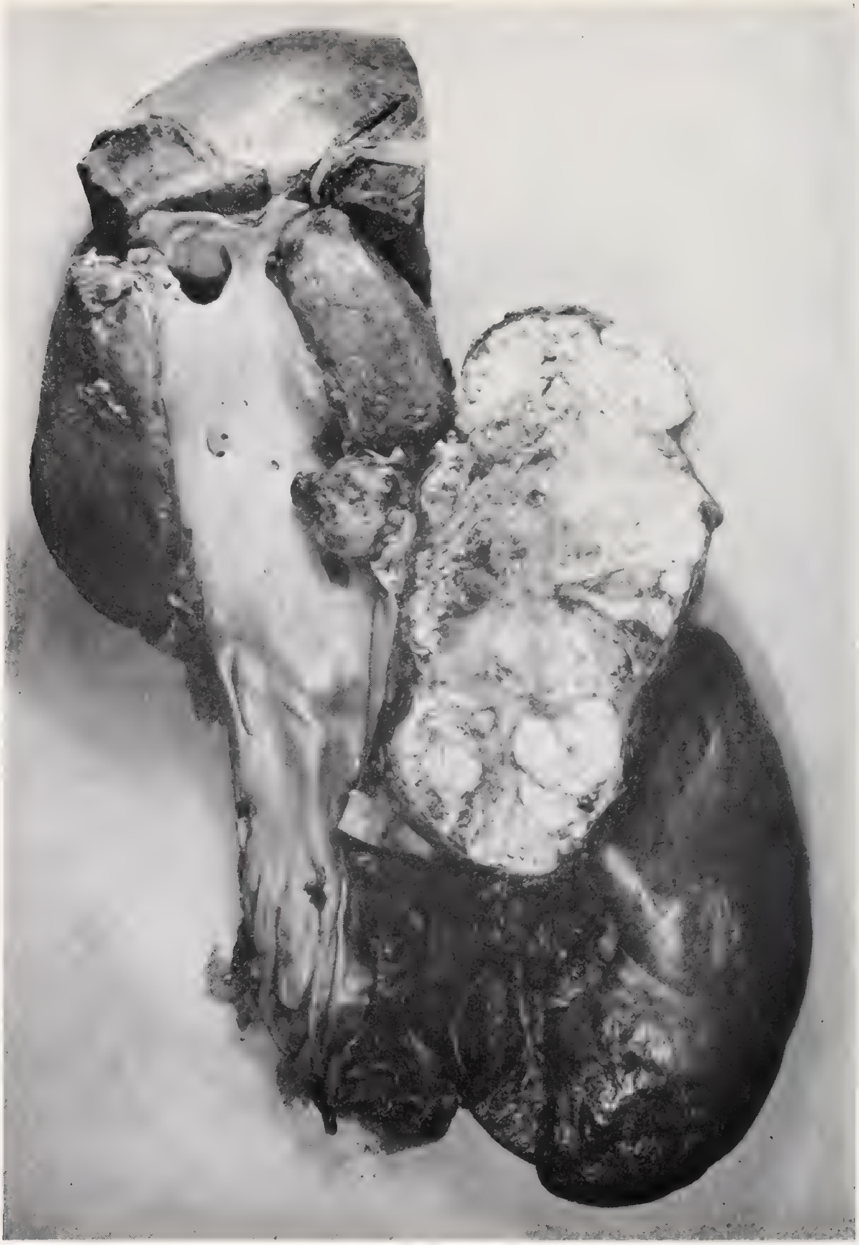

Fig. 13. Adrenal metastasis from renal carcinoma. Carcinomatous thrombus in the adrenal vein. (The primary renal carcinoma is documented in a separate picture, not reproduced here.)

is recognized as a classic contribution to renal pathology (32, 33, 34), and its precise gross and microscopic characterization still serves as the basis for the anatomic diagnosis of this disease. Although this was to remain Dr. Otani's only published article on the pathology of renal disease he maintained a deep interest in renal pathology; his often highly original and unique views became known only to his students. Having recognized glomerulosclerosis in diabetics long before its appearance in the literature (35) he considered this lesion as a manifestation of vascular sclerosis, i.e. arteriosclerosis in diabetes. His histologic criteria for the differential diagnosis of primary glomerular versus primary vascular disease of the kidney are still applied by his former students. For example, he called attention to the disappearance of glomeruli in chronic glomerulonephritis in contrast to vascular contracted kidney where the glomeruli are merely shrunken, but still visible and seemingly increased (crowded).

His views on Wilms' tumor are recorded as follows: "Wilms' tumor of the kidney in my opinion is a variant of malignant teratoma. In the usual Wilms' tumor one predominantly finds adenosarcomatous elements. Because of the admixture of striated muscle fibers some pathologists have preferred the designation embryoma or blastoma, and when growth of striated muscle predominates, rhabdomyosarcoma. The latter type of kidney tumor is a variant of Wilms' tumor."

This view was in keeping with the observation that a single tissue element may predominate in some malignant teratomas. He cited the following examples: "A sixteen year old girl had a large myxomatous ovarian tumor. Although this had been interpreted as a benign myxoma by another pathologist, I considered it a malignant teratoma with overwhelming development of myxomatous tissue. The patient died ten months later. In a young man, metastases from a malignant teratoma of the testis showed exclusively choriocarcinomatous growth. . . . Textbooks usually illustrate cases with multiple tissue elements as characteristic of malignant teratoma, but in daily practice we often see cases that differ from the textbook."

Dr. Otani's conservative approach to the interpretation of epithelial atypism in the uterine cervix is worth noting. The development of exfoliative cytology has led to early recognition of cervical carcinoma, but also to possible overdiagnosis of cervical malignancy. To many pathologists who consider these changes progressive, even slight atypism denotes a precancerous lesion. Dr. Otani did not agree with this concept of progression. To him, a lesion either was or was not a carcinoma. He drew the line somewhere through what is commonly called "carcinoma in situ"; most of these lesions he considered benign, while some he did accept as malignant, even though there was no trace of invasion. His ability to make this fine distinction was one of the unique and elusive qualities of his genius, but he never verbalized his criteria. His keen judgment is borne out by his follow-up data in sixteen patients whose initial biopsy had shown severe epithelial atypism which he had interpreted as benign hyperplastic changes. Of these patients, who received no further therapy, only one developed cervical carcinoma after a 10-year interval.

Many present day pathologists have again become more conservative in their evaluation of epithelial atypism of the cervix, because experience has shown that only a very small minority of atypical lesions progress to carcinoma.

It is regrettable that Dr. Otani did not record his vast experience with lymph node pathology, a field in which he excelled and where his judgment was frequently sought by his colleagues. He handled numerous consultation specimens, and seldom needed much time to arrive at a correct diagnosis. However, he usually wanted to know the location of the excised node and whether its enlargement was solitary. He was much more cautious in the interpretation of a solitary lymph node, because it might not adequately represent the disease. Also he took more pains with lymph nodes from the inguinal region. On infrequent occasions, when he could not make a conclusive diagnosis, he used the term "idiopathic lymphadenopathy," suggesting careful follow-up until the natural evolution of the disease attained clinical and histologic specificity.

Of particular interest are perhaps his views on the nature of Hodgkin's disease which he regarded as an inflammatory, granulomatous process. His views were in close agreement with those published by F. Mallory in 1914 (36), and he wrote some of these down in the following note: "... On examination of biopsied lymph nodes one sees cases with histologic features similar to those of Hodgkin's disease, but the most important, unique Sternberg giant cells are missing. Some pathologists will call these atypical Hodgkin's disease. However, in my opinion one should not accept this interpretation, otherwise this must lead to a change in concept of this disease, which will thus become a heterogeneous, almost nonspecific condition. ... Once I saw a lymph node without giant cells, which someone diagnosed as Hodgkin's disease. However, I doubted this diagnosis, and on further study found nucleated red blood cells. This led to a diagnosis of an erythroblastic type of acute leukemia. It could have been easily dismissed as atypical Hodgkin's disease, and the true diagnosis might not have been made. ... I often jokingly said, if the lesion is atypical Hodgkin's, it may not be Hodgkin's at all."

While most pathologists today accept the neoplastic concept of Hodgkin's disease, Dr. Otani may be remembered as a champion of the original concept of lymphogranulomatosis, which guided his judgement in the interpretation of isolated extranodal lesions removed surgically. He had seen a large number of such lesions in virtually every organ, and he comments as follows: "... The anatomical definition of Hodgkin's disease is a 'lymphogranulomatous' process with more or less generalized lymph node involvement. Once I saw Hodgkin's granuloma in a testicle removed for a tumor. The diagnosis was questioned because there were no palpable lymph nodes. I have always felt that when Hodgkin's granuloma happens to be found in an unusual location, the involved lymph nodes were hidden somewhere. In the above case, lymph nodes became palpable four months after orchiectomy. ..."

Dr. Otani did not adopt any of the histologic classifications of Hodgkin's disease which have come into common use (37–39), preferring the term "Hodgkin's disease," regardless of histologic variations. He believed that Hodgkin's disease is probably caused by an "unknown virus" without going into further speculations on its nature or implications for oncogenesis. In keeping with his viewpoint, he did not accept transformation of Hodgkin's disease into neoplastic lymphomas, but rather based claims of such occurrences on erroneous interpretation of the initial biopsy specimen. He cited examples of his own errors, for example, in the initial interpretation of a lymph node biopsy as Hodgkin's disease in a patient who subsequently died with reticulum cell lymphosarcoma: "... At the time of biopsy the lymph node contained multinucleated reticulum cells which resembled Reed-Sternberg cells. However, there were absolutely no eosinophils, and that should have been the warning sign. ..."

He emphasized that the presence of leukocytic, especially eosinophilic, infiltration is a valuable criterion in difficult cases.

His classification of malignant lymphomas, exclusive of Hodgkin's disease, is quite simple. He recognized two cell types, large and small, corresponding to reticulum cell sarcoma and lymphosarcoma, but admitted the existence of various intermediate forms. Life expectancy was shortest in cases with large, immature cells. He actually preferred the term "lymphosarcoma of reticulum cell type," because the large neoplastic cells failed to show the features of normal reticulum cells such as formation of reticular fibers. Giant follicular lymphoblastoma was recognized as a precursor of lymphosarcoma, with a comparatively long life expectancy.

Dr. Otani considered Ewing's sarcoma of bone as a form of reticulum cell sarcoma arising in bone marrow rather than lymph nodes. Lymph node involvement may occur later. "... Ewing's tumor is similar to other types of extranodal lymphosarcoma, where involvement of a visceral organ may precede that of lymph nodes. Like lymphosarcoma, Ewing's tumor may be multicentric and involve many bones at the same time. For this reason, amputation of a bone

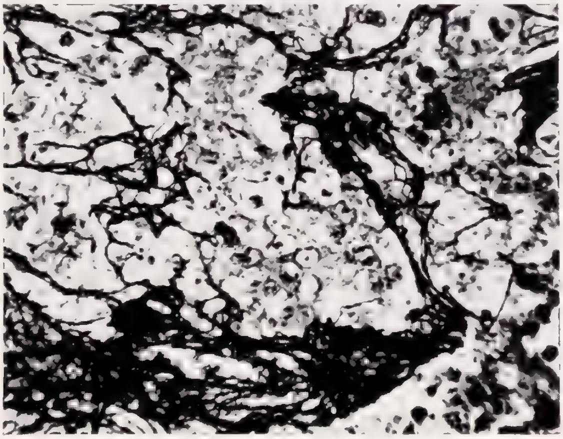

FIG. 14. Non-characteristic alveolar arrangement in a splenic lymphosarcoma.

FIGS. 14, 15, 16. Silver impregnation of reticulum fibers in neoplasms.

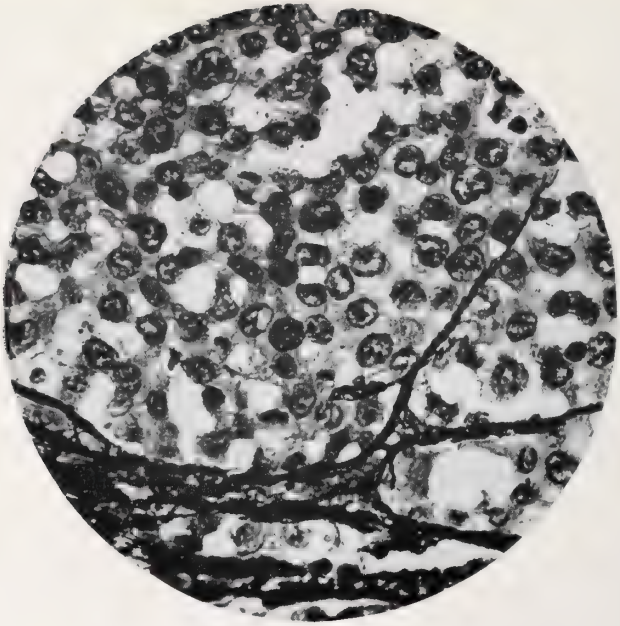

Fig. 15. Absence of fibers in reticulum cell lymphosarcoma.

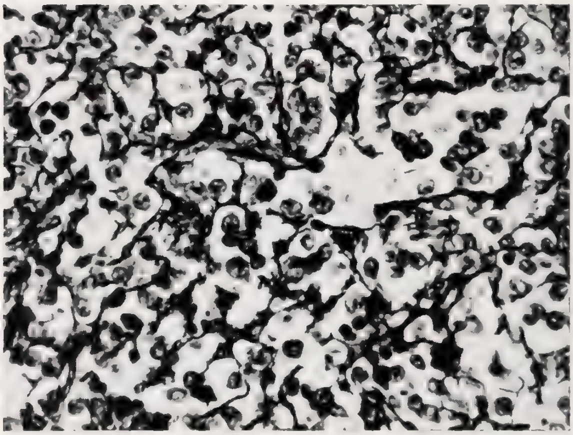

Fig. 16. Numerous fibers outlining small groups of cells in an anaplastic bronchial carcinoma.

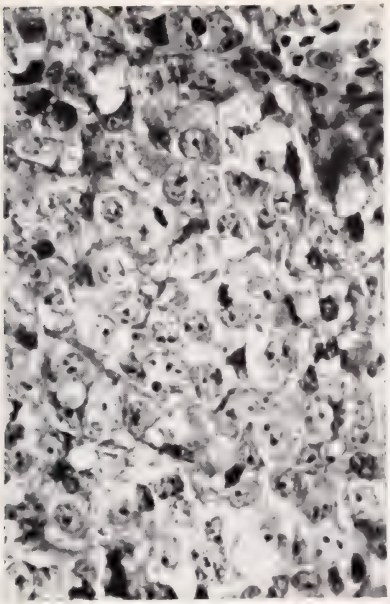

FIG. 17.

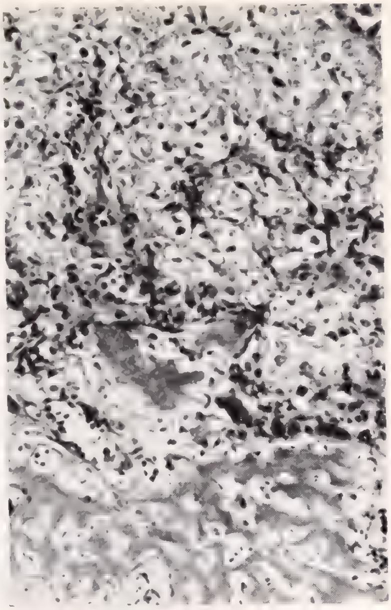

FIG. 18.

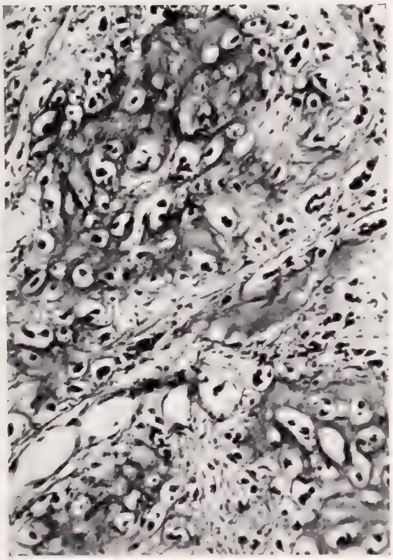

FIG. 19.

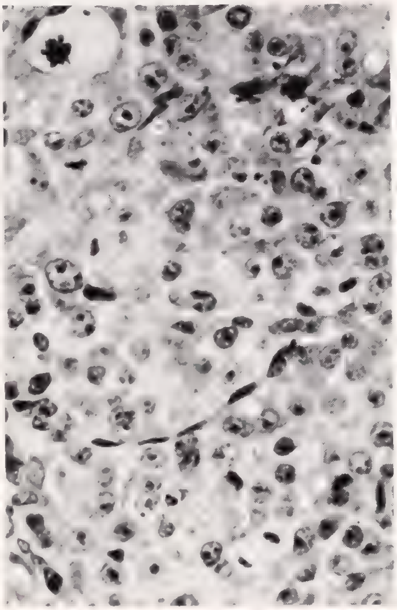

FIG. 20.

FIGS. 17, 18, 19, 20, 21, 22. Histological variations of Ewing's sarcoma in biopsies from the humerus. (Fig. 17, 18, 19), lymph node (Fig. 20) and in organs from autopsy—the ileum (Fig. 21) and the lung (Fig. 22).

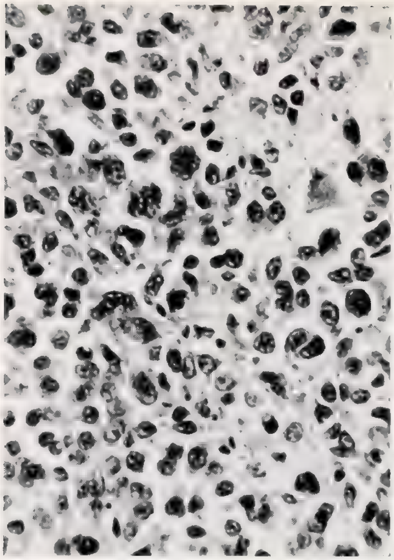

FIG. 21.

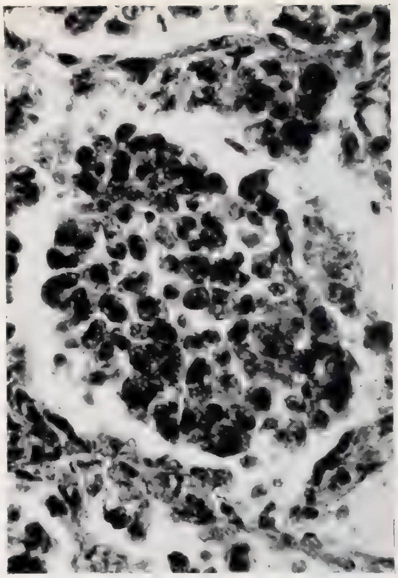

FIG. 22.

with Ewing's sarcoma is not advisable. . . . Some pathologists separate Ewing's sarcoma from reticulum cell sarcoma of bone (40). However to me they are one and the same tumor. Sometimes a nonosteogenic sarcoma originating in a bone, or a cellular angiosarcoma may be mistaken for Ewing's sarcoma. However, these tumors are radio-resistant, whereas Ewing's sarcoma is extremely radiosensitive. . . ."

Dr. Otani applied the term "benign lymphoma" to a circumscribed nodular collection of small mature lymphocytes, even when this attained a considerable size. Such collections are sometimes interpreted as hamartomas, particularly if they include other tissue elements. In his view, hamartomas do not undergo malignant transformation, while benign neoplasms may. Since benign lymphoma may on rare occasion turn into lymphosarcoma, it should be considered a benign neoplasm and not a hamartoma.

Dr. Otani, together with Dr. Ehrlich, first recognized eosinophilic granuloma of bone as a distinct entity (7) and pointed out its essentially benign nature. Even though his concept did not find ready acceptance by those who considered this bone lesion as a local manifestation of systemic histiocytoses, especially the Hand-Schüller-Christian syndrome (41, 42, 43) or "Histiocytosis X" as it was to be called later (44). Dr. Otani did not abandon his original point of view. In a concise article published in 1957, he discusses his criteria for the differentiation of eosinophilic granuloma of bone, Letterer-Siwe's disease, and Schüller-Christian's disease, documenting these with carefully chosen photographic illustrations from cases which he had personally studied in detail. While a unitary concept of the histiocytoses is still widely favored, some authors appear to be returning to Dr. Otani's original viewpoint on the basis of a thorough reappraisal of a large series of cases (45).

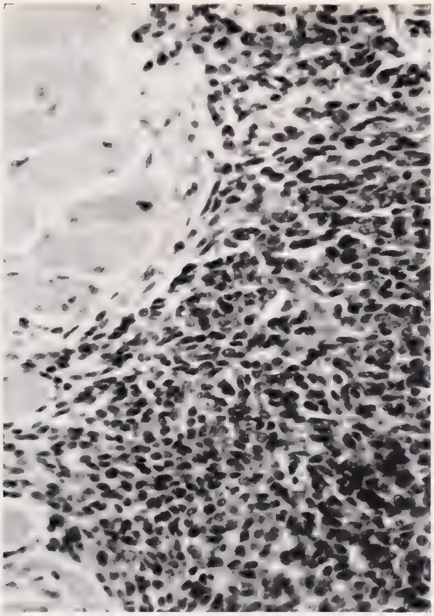

FIG. 23. Cellular angiosarcoma invading striated muscle.

On giant cell tumor of bone he wrote:

"Giant cell tumor of bone is essentially a benign tumor. Although malignant giant cell tumors have been reported, I have never observed this myself. In my opinion, the concept of malignant giant cell tumor is erroneous, for the following reasons:

1. Mistaken pathologic diagnosis: In several instances where a diagnosis of malignant giant cell tumor had been made I had the opportunity to review the slides, and my interpretation differed from that originally given, because the stromal cells had characteristics of spindle cell sarcoma, and there was no evidence of old hemorrhage. I considered these as examples of osteogenic sarcoma in which the biopsied area happened to contain many giant cells.
2. Mistaken x-ray diagnosis: The x-ray appearance may be atypical, especially if the giant cell tumor has broken through the cortex into the soft tissue. This may lead to an erroneous diagnosis of malignancy.
3. Mistaken clinical impression: In some cases the x-ray appearance of a lesion is considered to be typical for giant cell tumor, despite the fact that histological examination discloses a malignant growth of a different type.

Sixty or seventy years ago, not only giant cell tumors of the mandible or long bones, but also the so-called giant cell epulis was considered as sarcoma. For this reason, one may still see amputation specimens of long bones with such tumors in museums of pathology. Later, when follow-up studies disclosed absence of metastases in such cases, the diagnosis of

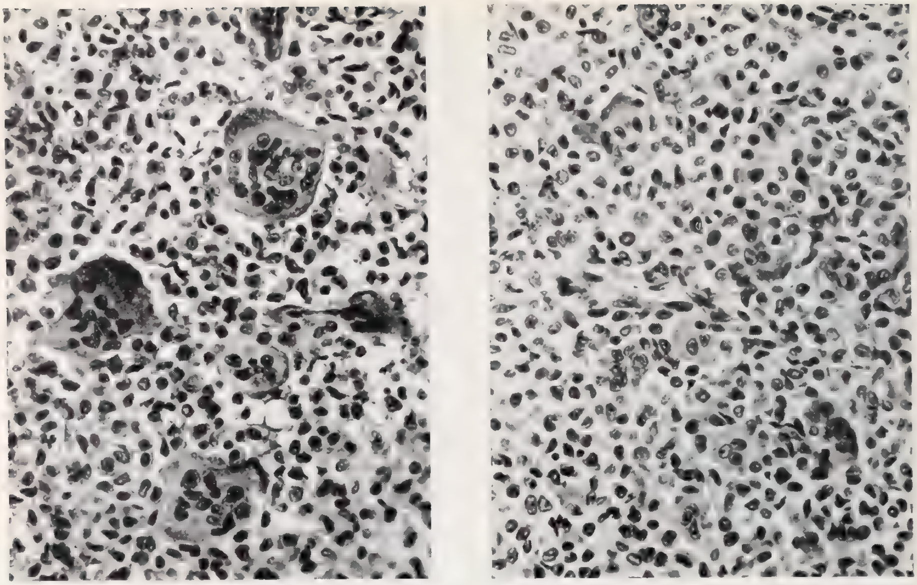

FIG. 24.

FIG. 25.

FIGS. 24 and 25. Giant cell tumor of bone. A biopsy from a 14 year old boy who developed sudden pain while playing baseball. Radiological diagnosis was "bone cyst" in the humerus. (Classical giant cells of osteoclastic type in Fig. 24 and giant cells of transitional type in Fig. 25.)

benign giant cell tumor became accepted, and treatment by curettage and replacement with bone chips was introduced about 40 years ago.

The curetted fragments histologically show numerous giant cells of the osteoclastic type, with a background of so-called stromal cells which have the appearance of swollen fibroblasts with double or triple nuclei suggestive of transition to giant cells. Fresh and old hemorrhages within the tumor are responsible for the characteristic brown color of the gross specimen. For this reason it used to be called "brown tumor," a term which is now applied to the bone lesions of hyperparathyroidism. Fragments of the tumor may be covered with stratified squamous epithelium because of its occasional encroachment on the overlying skin. Since the tumor is destructive of bone, it may destroy not only the bony trabeculae (explaining the frequent absence of bone spicules in biopsy material), but erode the cortex and expand into the adjacent soft tissue."

Dr. Otani exhibited interest in a lesion which is generally neglected and disdained, namely, sebaceous cyst. He believed that so-called calcifying epithelioma was the end result of proliferation and calcification of the epithelial lining of the cyst. He also raised the possibility that sebaceous cyst may give rise to subcutaneous squamous cell carcinoma which may be confused with a metastatic lesion. Similarly, he believed that certain cases of keratocarcinoma originate in a sebaceous cyst.

Any appreciation of Dr. Otani's professional life would be very incomplete

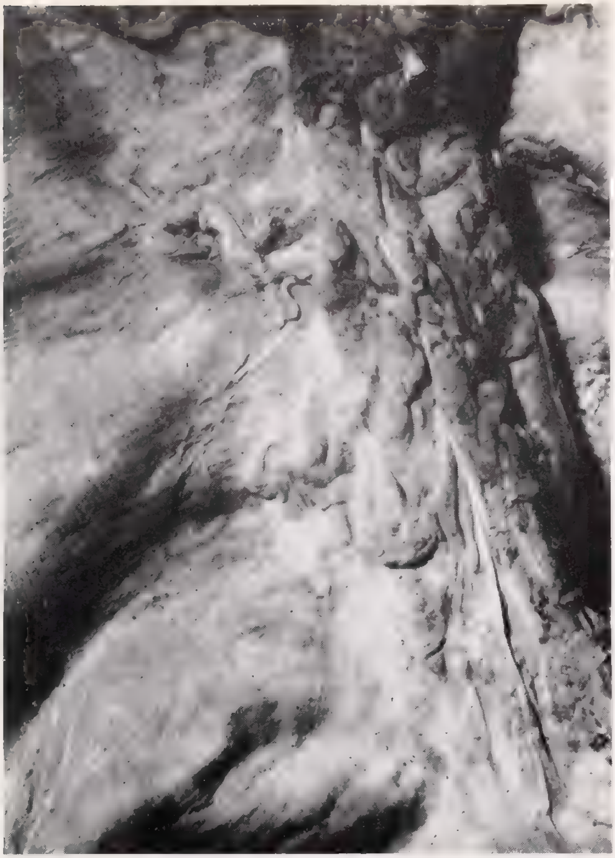

FIG. 26. Periarteritis nodosa in the gastric serosa. (Note an effective angle of lighting.)

without acknowledging his extraordinary skill and originality in photography and optical instrumentation. One must remember that when he started his professional career, photography of pathologic material was still in its infancy. Thus he became a pioneer in a new field, painstakingly working out technical improvements to a degree of perfection which only few can match today. He established something of an unofficial photography department where he personally made the gross and microscopic photographs for many publications by members of the hospital's staff. He was an excellent teacher of photography to those of his pupils who wanted to learn from him. When color photography became available, he promptly recognized its value for teaching pathology. In times when color film for hospital use was scarce, he succeeded in maintaining and augmenting the department's collection of color slides by virtue of his great photographic talent. Each carefully chosen exposure had to yield a picture that "told the story" and was as near technically perfect as possible. Thus he avoided waste that one could simply not afford.

At the same time he appreciated the limitations of photography and often

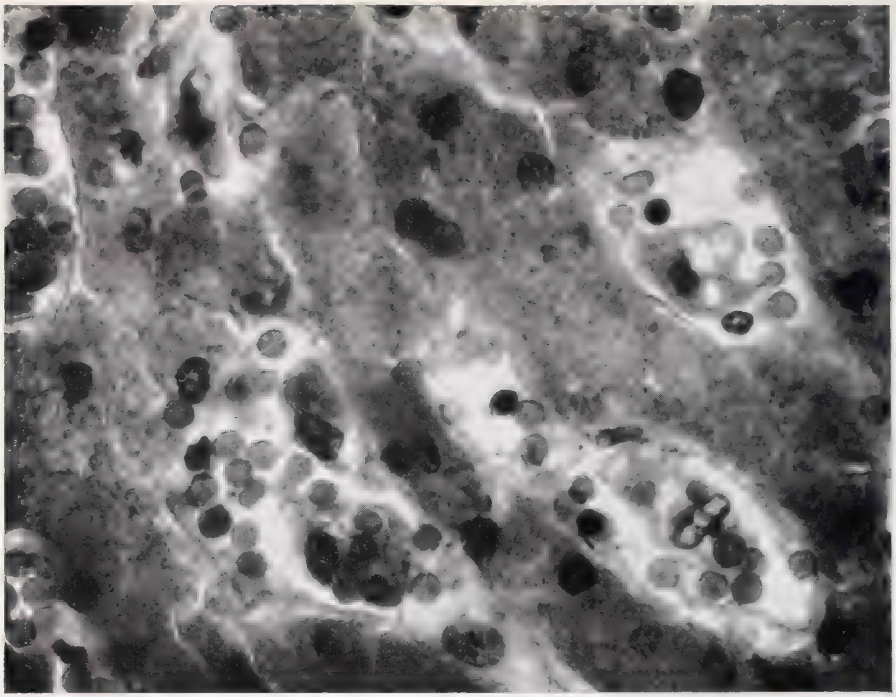

Fig. 27. Erythrophagocytosis by Kupfer cells in hemolytic jaundice (Note the stereoscopic appearance at high magnification, an effective illustration of this particular alteration.)

supplemented the photographs of gross specimens and of histological preparations with drawings. He was quite skillful in this medium and actually preferred it for illustration of fine histologic and cytologic details. He also encouraged his students to do likewise if only in a schematic manner.

He designed "Otani's box" for gross photography. Copied by many pathologists as well as by commercial establishments, this has been installed at many institutions throughout the country. It consisted of an inexpensive box with fixed photoflood lights and a single lens reflex camera on a movable stand. This was able to handle specimens in a wide range of sizes, and permitted careful composition of the picture. It was operated with a minimum of fuss requiring only focusing of the lens and setting of the diaphragm aperture.

Another ingenious instrument that he designed, was a prefocused ground glass viewer. This was used to project the enlarged image of a whole tissue slide, thus providing an intermediate step between the examination with the naked eye and low magnification microscopy. He encouraged the residents to learn photomicrography not only for the purpose of recording pathologic findings, but also as a means of self-education. He insisted that the residents pay for their own film to discourage waste and to enforce careful scrutiny of the slides before selecting an area to be photographed.

Since he considered photography as an integral part of the study of pathology he felt that it should not be relegated to technologists. He himself always tried for perfection which can only be attained by those who possess not only high technical skill but also a thorough understanding of the subject. Dr. Otani seldom used high magnifications. The vast majority of his photomicrographs were in a low to medium range, illustrating tissue rather than cellular changes. His ultimate goal was perfect reproduction on film of what the eye perceived. In trying to attain the impossible, he came as close to it as any man.

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Large, Sessile Mucosal Polyps of the Colon:

The Problem of Repeatedly Negative Biopsies

SADAO OTANI, M.D.

If repeated biopsies of a large, flat colonic polyp reveal a persistently benign morphology, a difficult problem may arise with reference to immediate surgical procedure. Crohn correctly pointed out that even if negative biopsies are obtained from a large colonic lesion that is clinically suspicious of malignancy, a radical resection should be performed. This general statement, although correct, does not specify what is meant by "clinically malignant."

Since a radical colonic resection is still a serious operation, many surgeons are unwilling to undertake drastic surgical measures on the basis of a biopsy report that does not indicate malignancy. This hesitation on the part of the surgeons is understandable. However, it has been our observation that this reluctant attitude, with subsequent delay in proper therapy, has been the cause of undesirable consequences in certain instances. Occasionally the surgeons have sufficient courage to resect a large sessile polyp despite a "benign" biopsy report. They do this with the knowledge that certain types of colonic and rectal polyps are potentially malignant.

As we will demonstrate, the resected specimens in most of these cases actually contained localized areas of malignant transformation. The fact that adenomatous polyps of the large intestine undergo malignant transformation is well known. The early focus of dedifferentiation, although it may occur anywhere within the polyp, often occurs in the central regions. The usual biopsy taken from the periphery of the lesion will not, therefore, reflect the malignant changes. It is obvious that repeatedly negative biopsies can be obtained from a malignant polyp.

It seems to us, however, these simple facts have not been thoroughly appreciated by all surgeons. This is perhaps due mainly to a lack of a clear-cut discussion of this problem in the literature, although innumerable papers dealing with rectal and colonic polyps in general have been published. It is the main purpose of this paper to describe our views, gained by our own experiences as surgical pathologists, in an attempt to clarify this perplexing problem.

Definition and Classification

The mucosal or adenomatous polyp is by definition a benign neoplasm of glandular origin. The ensuing discussion relates to this tumor and not to those of connective tissue origin. Polyps of the large intestine have been subjected to elaborate classifications by Schmieden and Westhues (1), and by Fitzgibbon and Rankin (2). These classifications are considered of limited value by more

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From the Department of Pathology, Mount Sinai School of Medicine of The City University of New York, N. Y. 10029; Previously unpublished paper written approximately 1948; Edited by Lotte Strauss, M.D. and Mamoru Kaneko, M.D.

recent authors, who stress the basic similarity of all adenomatous colonic polyps and who tend to consider all polyps of the large intestine as premalignant lesions (3–5). These generalizations are prompted by the fact that at our present level of knowledge, we have no single gross or microscopic criterion by which we can evaluate the malignant potentialities of a given polyp (6). It becomes necessary, therefore, to employ a statistical approach to this problem.

Although our study is not evaluated statistically, it is our experience that the frequency with which large, sessile adenomatous polyps of the large intestine have been found to be malignant, despite "negative" biopsies, warrants their complete eradication by techniques sufficient to prevent recurrence.

Criteria of Malignancy

The acknowledged gross criteria of malignancy of a mucosal polyp include focal induration, fixation of the tumor to the submucosa, and ulceration of the mucosal surface. Although these findings are valuable indices of malignancy when present, it is a commonplace experience to find microscopic evidence of malignant transformation in mucosal polyps in the absence of grossly suggestive changes.

The microscopic criteria of malignancy, as elaborated by Swinton (10), include anaplasia, irregularity of the architecture, and invasion. One cannot take issue with the validity of these criteria. However, except for definite lymphatic or vascular invasion, they are subject to wide personal interpretation. This factor is responsible for much confusion both in the reporting of biopsy and in subsequent therapy.

Although a diagnosis of "carcinoma" on a rectal biopsy may be considered a desirable precursor to radical resection of a large bowel, we do not consider it a necessary prerequisite. As we will demonstrate, the gross appearance of the tumor combined with the histologic pattern of the tissue should be a sufficient indication.

Cases Illustrative of the Problems Presented by Sessile Polyps

Case 1 (#47736). This case demonstrated the fallacy of temporizing with a sessile polyp. The tumor, a sessile polypoid mass in the recto-sigmoid, was biopsied on two occasions at a one-week interval. In each instance the biopsied tissue was composed of clusters of delicate, villous processes consisting of a thin core of vascular connective tissue covered by single and multiple layers of elongated mucus-secreting columnar cells. In each instance, the report was "villous adenoma." After an interval of three months, during which time no therapy was administered, the tumor was resected because the bulky mass actually caused obstructive symptoms.

The resected specimen was a large, soft, sessile mucosal polyp measuring 10 cm in diameter. The surface of the polyp was covered by a carpet of delicate papillary processes. Microscopic study at this time revealed focal carcinomatous transformation within the adenomatous polyp with metastases to the regional lymph nodes.

Case 2 (#P-19489). In this case we do not have a biopsy history. The points illustrated are: The villous adenoma, though almost always a soft, sessile tumor, may not have a characteristic surface appearance; and the location of carcinomatous transformation is central and inaccessible to biopsy.

The resected tumor was a colonic polyp measuring 7 cm in diameter. The surface was finely and coarsely lobulated and did not reveal the villous structure which was seen histologically (Fig. 1a). The low-power photomicrograph (Fig. 1b) demonstrates the single central focus of carcinomatous transformation within an otherwise histologically benign villous adenoma. A single lymph node metastasis was found. One, or even multiple, biopsies from the periphery of this tumor would have shown a benign adenomatous pattern and would certainly have been a misleading guide to therapy unless the potentialities inherent in this gross and microscopic pattern were thoroughly appreciated (Fig. 1c and d).

Case 3 (*#101513*). This is another example of the type of polypoid lesion seen in case 2. The resected specimen was a soft, rounded mucosal polyp of the sigmoid measuring 5 cm in diameter. The surface was coarsely lobulated and the villous pattern is not in evidence grossly. There was a central focus of carcinomatous transformation with infiltration.

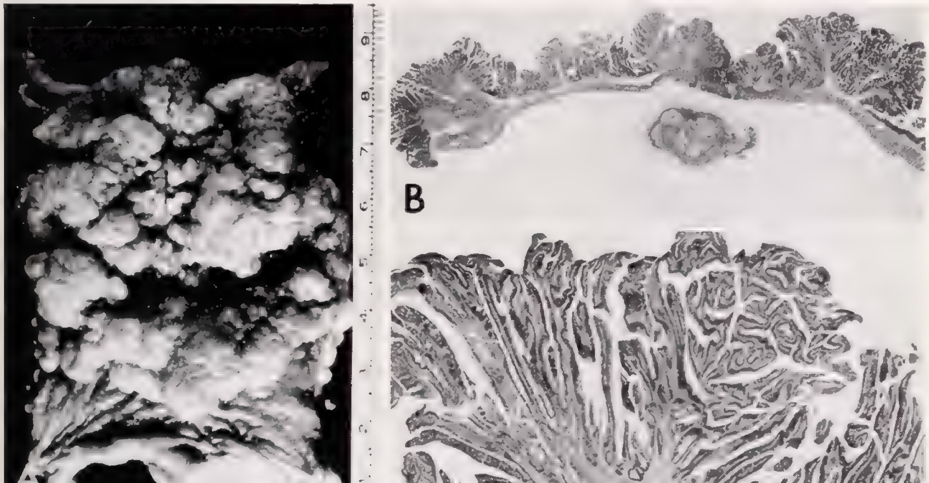

FIG. 1. Case 2. (a) Large flat villous adenoma. (b) Entire cross section of tumor showing villous type of structure. Localized carcinoma in central portion and one involved lymph node. (c) Papillary structure. (d) Elongated papillae but less mucus production than Case 1. (e) Area of infiltrating carcinoma.

Case 4 (*#P-43738*). The insidious nature of the villous type of lesion is illustrated by the case of a middle-aged woman who consulted a gynecologist because of vaginal bleeding. A soft polypoid tumor on the posterior wall of the vagina was discovered and biopsied. The report submitted by another laboratory was "adenocarcinoma." Upon further examination a soft, sessile polypoid lesion was identified in the anterior wall of the rectum. The rectum, vagina, uterus and adnexae were resected. Examination of the specimen revealed a typical "villous adenoma" measuring 11 cm in diameter in the anterior wall of the lower end of the rectum. Transsection of the tumor revealed an invading carcinoma which infiltrated through the wall of the rectum into the vagina.

Case 5 (*#73150*). This case demonstrated an interesting variation in the gross appearance of the sessile villous adenoma, and shows once again the central focus of carcinomatous transformation.

The resected specimen was a flat, polypoid mass from the rectum measuring 7 cm in diameter. The polyp was uniformly soft and characterized by a coarse type of lobulation which was highly suggestive of giant rugal folds (Fig. 2a). The villous nature of the tumor which can be seen in the low-power photomicrographs (Fig. 2b and e) was not grossly apparent. Here, too, note the isolated small focus of carcinomatous transformation in the central portion of the polyp (Fig. 2c and d), whereas the remainder of the tumor is histologically benign. A biopsy from the periphery of this tumor could not have revealed the isolated carcinomatous focus.

Case 6 (*#92750*). This is another example of a flat adenoma with a giant rugal pattern. The resected specimen was a sessile mucosal polyp of the sigmoid measuring 12 cm in diameter. The surface was coarsely lobulated and folded in the manner of giant rugae. Foci of delicate villous processes were seen on the peripheral surfaces of the tumor. The center of the tumor was indurated, and microscopic study revealed carcinomatous transformation within the area of induration.

Case 7 (*#P-20575*). Because we are impressed with the malignant potentialities of the villous adenoma, we recommend prompt segmental resection of the lesion when it is recognized clinically by its gross appearance.

This tumor, a soft, finely lobulated sessile polyp measuring 10 cm in diameter, was resected without recourse to biopsy. Note the superficial covering of delicate papillary processes, which when present readily identify the tumor. Microscopic examination of the tumor revealed no evidence of infiltration (Fig. 3b). The histologic structure was that of a villous adenoma with scattered foci of proliferative activity and nuclear hyperchromasia suggestive of beginning carcinomatous transformation (Fig. 3e). Despite the absence of infiltration in this specimen, we feel that the radical resection was not only warranted but definitely indicated by the gross appearance of the polyp.

Case 8 (*#P-43443*). This is an example of a sessile polyp of somewhat unusual gross appearance, which was resected because two biopsies of the tumor revealed the histologic pattern of villous adenoma.

The resected specimen was a soft, round sessile polyp measuring 7 cm in diameter. The surface of the polyp was smooth and a fine lobulation is barely perceptible (Fig. 4b). Despite the misleading gross appearance, the histology of this tumor was typical of villous adenoma (Fig. 4a and c). In this case as in case 7, no malignant change was found within the resected polyp. However, as these examples demonstrate, the resection was entirely justified.

Case 9 (*#P-39690*). This case represents another example of a sessile polypoid tumor of the large bowel resected because the histology of the biopsied tissue was that of potentially malignant villous adenoma.

The resected specimen was a soft, sessile polyp measuring 5 cm in diameter. The surface was coarsely lobulated and had a giant rugal pattern which is seen in this type of tumor. Villous processes were not grossly obvious. Microscopically the entire lesion was of benign character, but the elongated filiform processes of the villous adenoma were readily identified.

These last three cases demonstrate three different, single sessile colonic polyps which

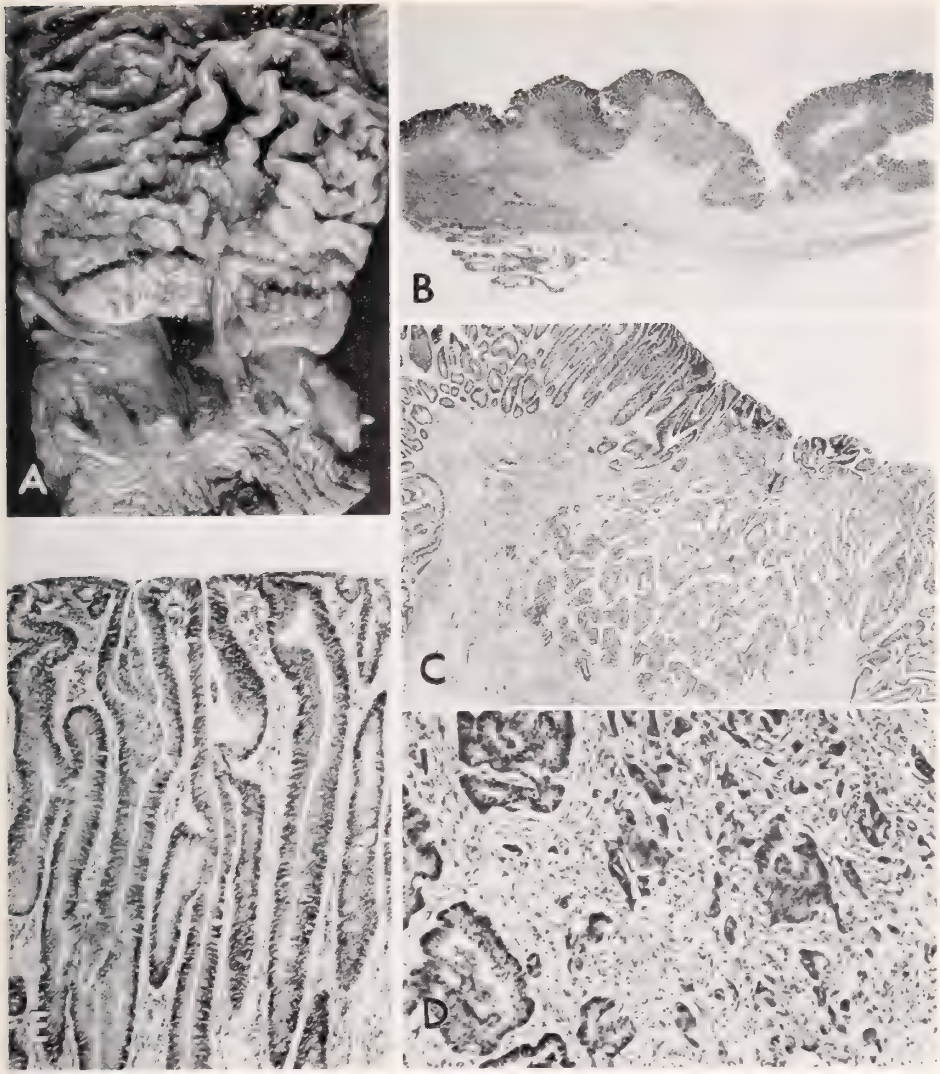

Fig. 2. Case 5. (a) Resected specimen. Note surface of giant-rugae type. (b) Low power photomicrograph of entire specimen showing small localized infiltrating carcinoma in central area. (c) Higher magnification of carcinomatous area. (d) Higher magnification of carcinomatous area. (e) Papillary structure of nonmalignant portion of tumor.

were resected because the gross appearance of the polyps and the histology of the biopsied tissue in each case represented a pattern which experience has taught us to consider of high malignant potential. Grossly the tumors were similar in that they were flat, soft and sessile. They differed, however, in surface configuration—one being finely lobular and papillary in appearance, another being relatively smooth, and the third having a giant rugal pattern. Despite the variations in gross appearance, each of the tumors was a villous adenoma histologically.

Case 10 (101514). A large sessile polyp of the sigmoid colon was biopsied. Microscopic examination of the tissue revealed an histologic pattern of villous adenoma (Fig. 5a). The

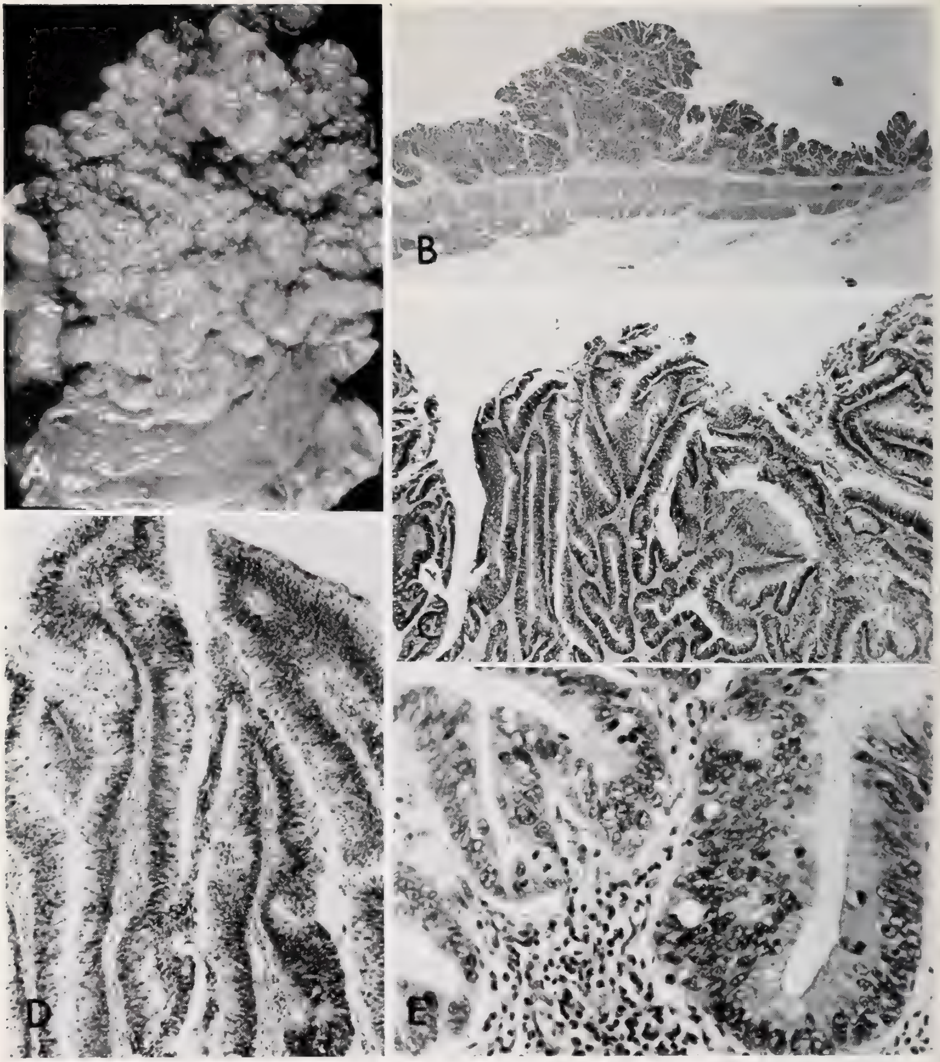

Fig. 3. Case 7. (a) Resected specimen. Flat, large villous adenoma without malignant transformation. (b) Cross section of tumor. Note absence of tumor infiltration. (c) and (d) Papillary structure. (e) Photomicrograph taken from base of tumor at center. Glandular structure showing considerable cellular irregularity and occasional mitoses.

report "villous adenoma" was returned to the surgeon. At a subsequent operation the tumor was simply stripped from the muscularis and delivered through the anus because the report was construed to indicate a conservative approach.

The gross specimen consisted of a soft villous adenoma 8 cm in diameter, sitting on a thin strip of submucosa (Fig. 5b and c). Microscopic examination revealed a single central focus of carcinomatous transformation (Fig. 5c and d). Because of the misinterpretation of the report, an additional radical operation had to be undertaken.

Case 11 (M-3971). In August of 1946, a soft, flat tumor of the rectum was biopsied. The histologic appearance of the tumor was characteristic of villous adenoma and was so

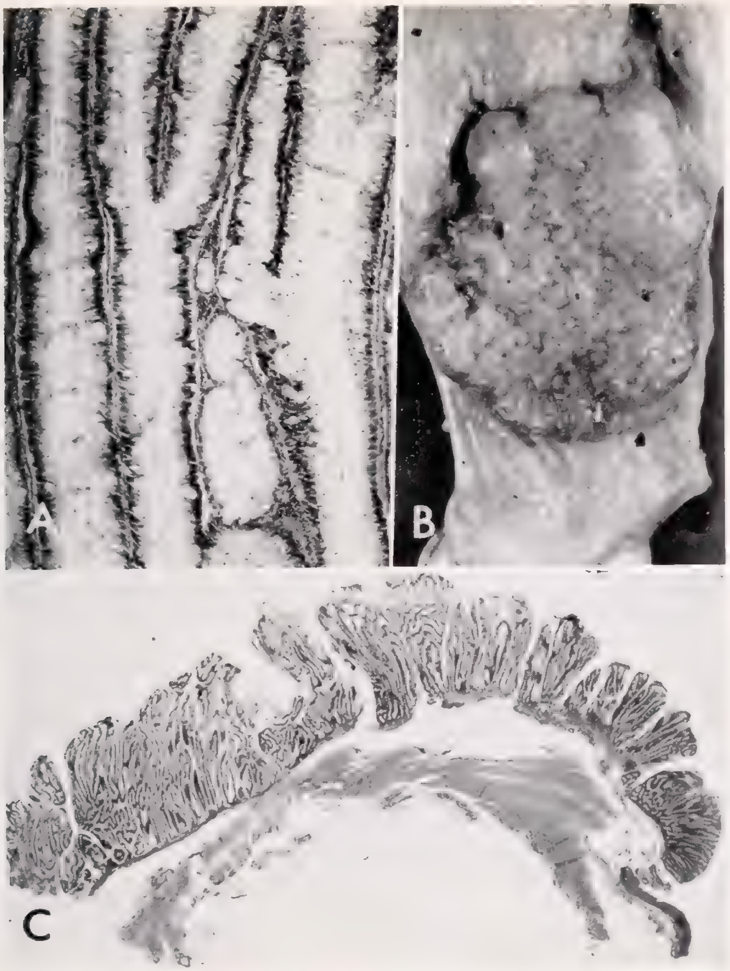

FIG. 4. Case 8. (a) One of two biopsies. Reported "villous adenoma, potentially malignant." (b) Resected specimen. Large flat adenoma with smooth surface. (c) Cross section of part of tumor. Note absence of invasion. Villous structure clearly seen.

reported. The surgeon was advised to resect the tumor because it was considered potentially malignant. However, he was unwilling to perform radical surgery in the absence of a definite report of malignancy. The tumor was fulgurated but subsequently recurred. Three additional biopsies within the following two years revealed an histologic picture identical with that of the initial biopsy. The fifth biopsy done in August, 1948, however, revealed a clear cut adenocarcinomatous area in addition to villous adenoma. When the patient was promptly operated on for the tumor, metastases to the liver were found.

Conclusions

1. Examples of malignant and potentially malignant, large, flat villous adenomas of the recto-sigmoid are presented.
2. Macroscopically, despite a basic similarity, these tumors present certain

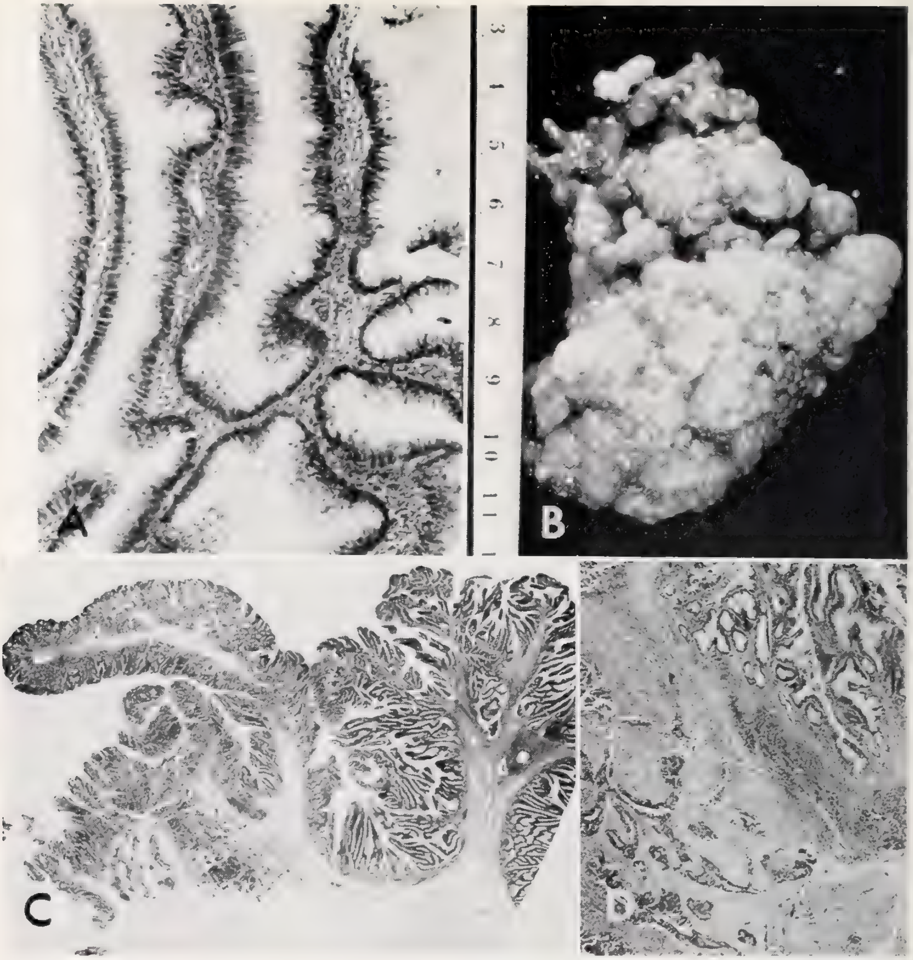

FIG. 5. Case 10. (a) One of two biopsies reported "villous adenoma." (b) Removed specimen stripped from muscularis. Small carcinomatous area found in central portion of specimen. (c) Left lower corner showing carcinoma. (d) Infiltration of carcinoma.

striking variations in surface appearance. Some are finely lobular and papillary in appearance, others are coarsely lobular and have a surface pattern resembling giant rugae, and still others have a relatively smooth surface.

3. Histologically these tumors, despite variations in gross appearance, have a consistent and unique structure of elongated delicate papillary processes with a thin core of vascular connective tissue that is covered by a layer of mucus-secreting columnar epithelium. Often numerous nuclei are closely packed at the base. These characteristics should be interpreted as potentially malignant.

4. When a tumor in the recto-sigmoid region has the gross appearance as described above and histologically fits into the villous adenoma pattern, the lesion should be considered potentially malignant and a radical resection of the

lesion should be performed. This should be done despite the fact that one or more biopsies from the tumor may fail to reveal evidence of malignancy.

5. Negative biopsies are so frequently obtained in these tumors, because the focus of carcinomatous transformation is persistently central in location.

6. Two cases are presented in which this malignant potential of villous adenoma was either ignored or not properly appreciated with undesirable consequences for the patients.

(Ed. note: Dr. Otani's original manuscript included five additional plates of photographic illustrations which we have reluctantly omitted because of limitation of space.)

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Malignant Melanoma

SADAO OTANI, M.D.

It is well known that some small malignant melanomas may produce extensive metastases, and regretfully we see too many cases of this type every year.

It is obvious that if one recognizes their true nature early and they are widely excised one may be able to avoid the calamity of hopeless spread. It would seem that unlike those deep-seated tumors, as in lung or pancreas, melanomas located, as the great majority are, on the skin could be detected early; but this is not always the case. Pathologists not infrequently receive tissue from melanomatous metastases before the primary lesion is detected. Why are these primary melanomas overlooked? There are perhaps several reasons:

1) Very tiny size. An example of such a case came to me when enlarged axillary lymph nodes were submitted for examination and proved to be metastatic melanoma. The primary tumor was searched for in the corresponding areas by four surgeons, who could not find it. Only five weeks later a tiny melanoma was found on the back almost in the midline.

2) Obscure location. Difficulty in detecting these lesions is not only because of extremely small size, but also because it is in a location where such a lesion is covered by other tissue or concealed by position, for example, on the head, in the nail bed, behind the ear, in the nasal vestibule, the vagina or anus, and even behind the knee.

3) Absence or scantiness of pigment. This is a source of difficulty in identification, particularly on the sole of foot, or where ulceration produces the appearance of granulation tissue.

4) Innocent, benign appearance. Insignificant appearance as of a benign nevus has led in the past to fulguration or excision without histologic examination. The incident has then been forgotten. When many years later metastatic melanoma was found, only persistent inquiry disclosed the history.

It should be emphasized that malignant melanoma can be diagnosed correctly only by histologic examination. If a pigmented nevus shows a relatively rapid increase in size it should be regarded with suspicion of malignancy, whatever the total dimension. This is especially so if it is located at a point of constant pressure or irritation, for example the sole of the foot, or on the trunk where a girdle pressed constantly on the nevus. Such a suspect nevus should be widely excised without biopsy. Why wide excision? The following examples may suffice.

A tiny, malignant melanoma had been excised a year before. Multiple recurrent nodules occurred around the scar. A wider excision might have avoided this recurrence. In another case, what was considered too close an excision elicited the recommendation that wider excision be carried out; however, this

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was done four months later. Then the re-excised tissue contained two small, but already visible melanomatous masses.

In recent years a very radical operation, regional lymph node dissection, has been stressed. In one case I will cite, after removal of a melanoma of the vulva, radical lymphadenectomy was carried out. After a year there was recurrence at the site of the primary tumor. This indicates that the local excision was not wide enough.

The histologic structure of melanomas is most complex. If pigment is

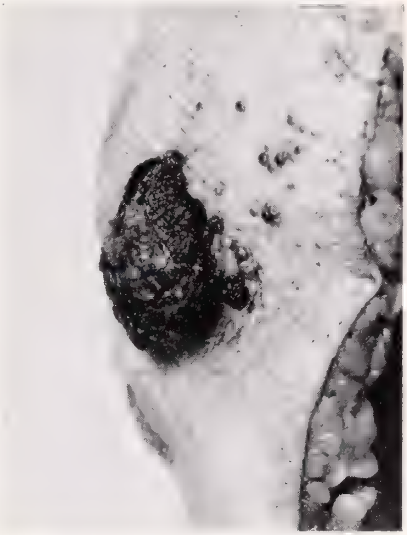

FIG. 1: Melanocarcinoma in thigh. Note spread of tumor in adjacent skin. A lemon-sized metastatic node was also found.

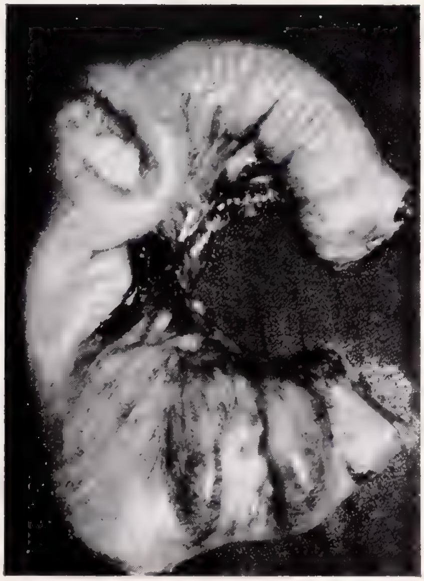

FIG. 2: Metastatic melanoma in ileum.

present the diagnosis is usually simple. It is the so-called nonpigmented melanoma that provides a diagnostic problem and in which the wrong diagnosis is made.

Here is an example: A small tumor nodule was removed from the sole of the foot below the ankle of a 26-year-old man. It was diagnosed as a fibrosarcoma. A few months later it recurred. The same surgeon reoperated and radiotherapy was given. At this point I was asked to see the section. The tumor consisted of spindle cells without a trace of pigment. It did, indeed, have much of the appearance of a fibrosarcoma, but on the basis of experience I was inclined to

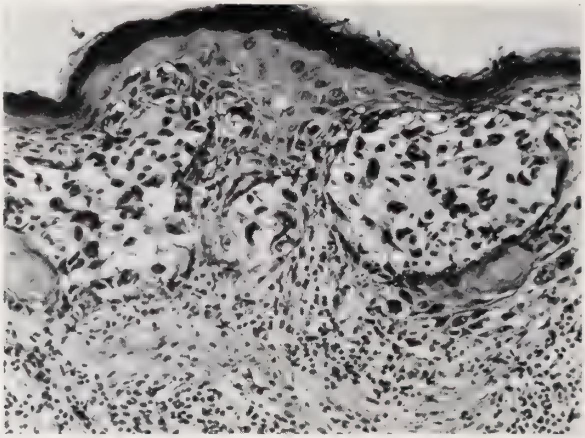

Fig. 3: Early malignant melanoma.

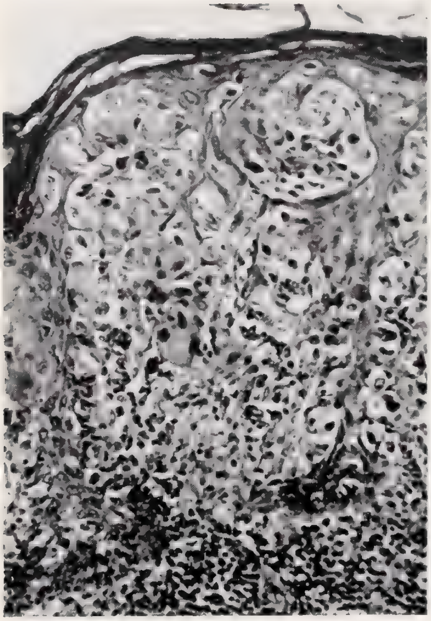

Fig. 4: Malignant melanoma with invasion of dermis and epidermis.

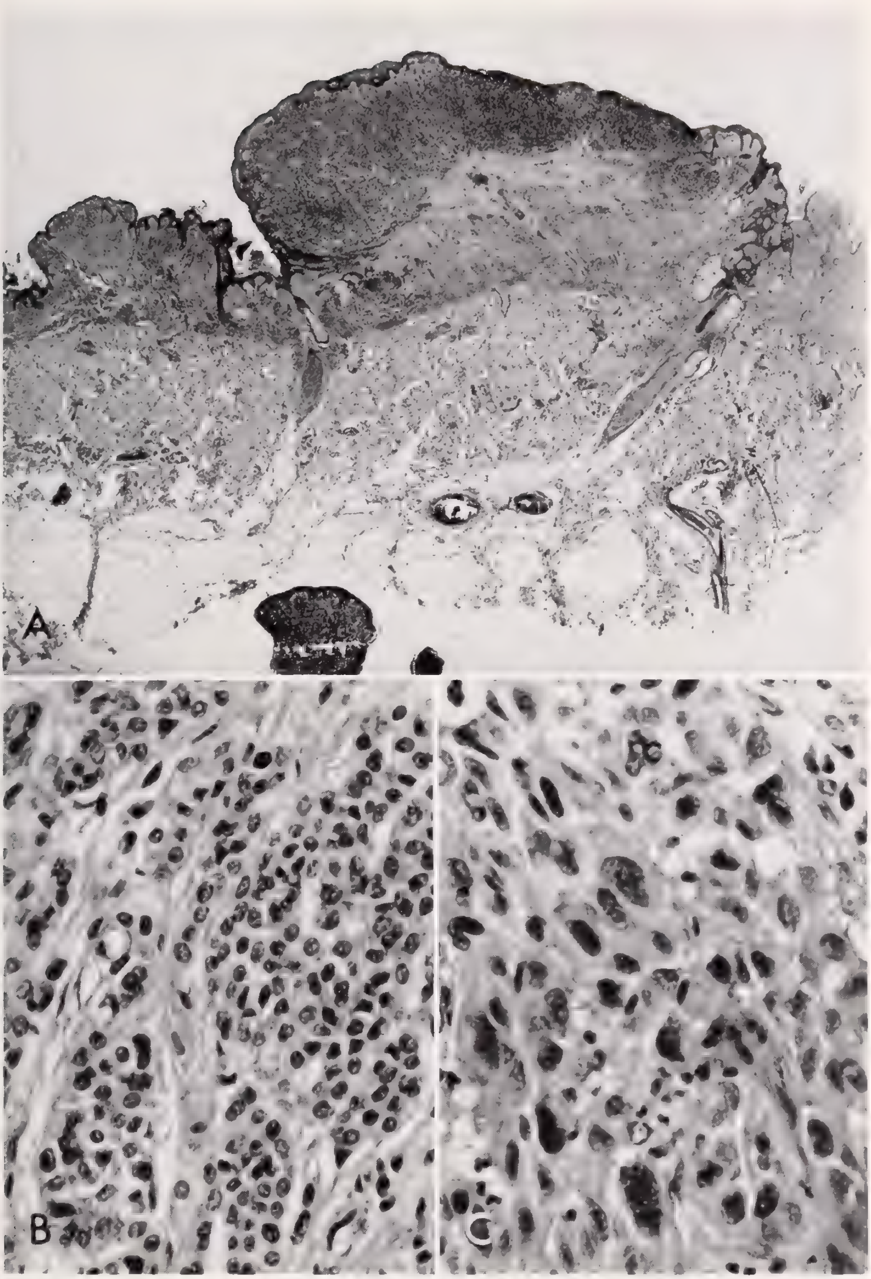

FIG. 5: (A) Melanocarcinoma arising in a nevus present since birth. Patient 40 years of age. (B) Benign nevus area. (C) Area of malignant change.

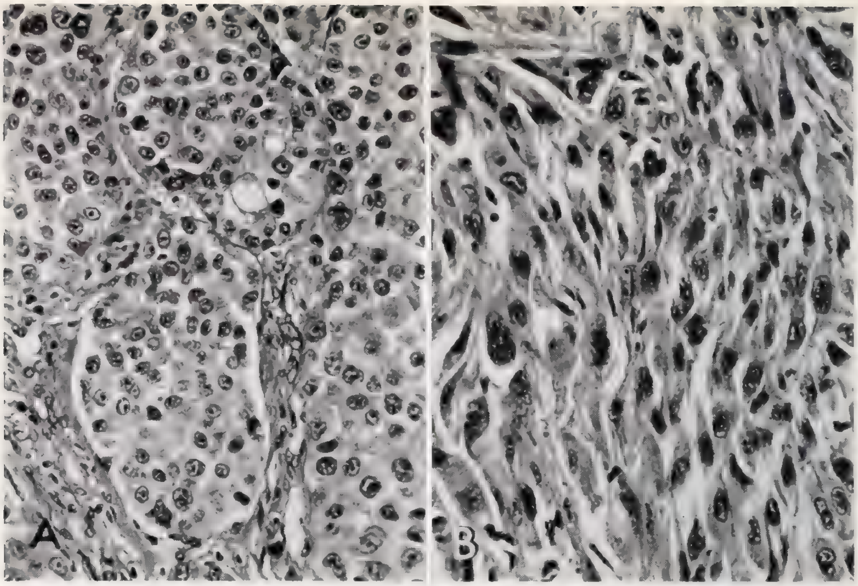

FIG. 6: (A) Metastatic melanoma in lymph node showing a usual alveolar structure. (B) Area from same section as A, showing a spindle cell character.

believe it to be a melanoma. An amputation and removal of all possible lymph nodes was carried out. Although no lymph node metastases were encountered the patient died within two years. Autopsy disclosed multiple grayish-white metastatic nodules. Intensive search for pigment revealed a very small pigmented focus in one nodule. Thus essentially because of the absence of pigment an erroneous diagnosis was made and the wrong treatment given.

However, on a more cheerful note, an almost identical case diagnosed correctly and treated promptly with amputation and lymph node dissection has been followed for seven years without recurrence.

Although metastatic tumors are, in general, multiple, there are exceptions. Solitary metastasis does occur on rare occasions. Perhaps the most frequent and striking examples occur in hypernephroma. This phenomenon can be observed in melanoma also.

As an example, an ovarian tumor mass was removed in a 35-year-old patient; it proved to be a metastatic melanoma. Subsequent inquiry disclosed that a small pedunculated mole had been removed from her back 16 years before. She is apparently healthy otherwise.

A question may be raised here. Is this tumor of the ovary truly metastatic? In order to accept this concept it has to be assumed that at least one melanoma cell reached the ovary 16 years before. Here it multiplied.

Melanoma is a very malignant tumor. Why did this particular melanoma grow so slowly? After studying numerous cases we have to accept the existence of two types: fast-growing and slow-growing. However, between them no histologic differences can be demonstrated. However, there must be some biological difference. Some biologic factor, perhaps hormonal, may exist in certain individuals which inhibits the growth of tumor cells.

This peculiar latent, or long silent metastasis or late recurrence is well known in other carcinomas as well. Recently I observed recurrence of breast carcinoma in the scar 26 years after radical mastectomy. Such latency is perhaps a little more common in melanoma than in any other carcinoma. I have seen many cases of this type. The longest free interval before recurrence of a melanoma was 22 years following removal.

I am of the opinion that surgical removal of a latent solitary metastasis is justifiable. Other metastases may be hidden in unknown locations but these, too, may be of a slow growing nature. The patient's life may be thus prolonged.

In recent years articles regarding the so-called juvenile melanoma have been published. It is said that it pursues a benign clinical course although its histologic appearance suggests malignancy. However, it must be remembered, that though rare, true malignant melanoma does occur in children. A colonic carcinoma is also exceedingly rare in children, but may also occur. Some melanomas in childhood were considered benign because of the age, however I considered them microscopically malignant.

Finally I recognize that while it is easy for us as pathologists to recommend wide excision, when the lesion is located on the face who has the courage to remove half of a patient's face? In some instances the dilemma is insoluble.

Comment

MILTON KANNERSTEIN, M.D.

This brief exposition of certain clinico-pathologic facets of the malignant melanoma problem was delivered by Dr. Otani as a talk to a general audience of physicians at another hospital in 1950. The points made are still relevant. In reference to the term juvenile melanoma, the differences implied are semantic, and some other pathologists also have eschewed the term because of the connotation of the word melanoma, despite the adjective juvenile. They prefer to call this appearance spindle cell or epithelioid nevus. However, Dr. Otani always emphasized the occurence, rare though it is, of true malignant melanoma in childhood, and the danger of extending the concept of bizarre juvenile nevi too far.

Excerpts from "Pathology of the Breast"*

SADAO OTANI, M.D.

General Considerations

Any palpable mass in the breast should be regarded as possibly malignant until proved otherwise. At no time should one depend on one's clinical impression. Even the youth of the patient should not alter this attitude. For instance, a 23-year-old woman was told she should ignore a nodule that she herself had discovered in her breast. Mainly because of her age the surgeon considered it a fibroadenoma. One year later at operation the mass was proved to be a carcinoma with metastasis to several axillary lymph nodes. She died within a year of extensive metastasis. As another example of avoiding a false sense of security, long-known duration should not be regarded as indicating a benign nature. A breast nodule known by the patient to have been present for more than ten years turned out, upon removal, to be a carcinoma.

Even in the presence of so-called chronic cystic mastitis, which is known as a benign lesion, coincidental carcinoma may exist, and clinically resembling a cyst, prove to be a carcinoma with cystic degeneration.

Thus, it is of the utmost importance that a mass within the breast be removed surgically for pathologic examination.

Chronic Cystic Mastitis

In rare instances an extremely hard mass within the lesions of mastitis may simulate scirrhous carcinoma. The reason for this induration may not be apparent. But, as in linitis plastica of the stomach, carcinoma cells may be difficult to identify in densely fibrous tissue, so that these densely fibrous areas in mastitis should be examined with great care.

Carcinoma found Coincidentally in Chronic Cystic Mastitis

The relationship between chronic cystic mastitis and malignancy has often been raised, namely whether chronic cystic mastitis is a forerunner of carcinoma. It appears to me that carcinoma found in chronic cystic mastitis is coincidental and that the latter is not to be regarded as a cause of carcinoma. Nevertheless, in the breast mass removed for frozen section one should take the utmost care not to overlook a small carcinoma (Fig. 1).

There exists a considerable difference of opinion among pathologists as to the incidence of carcinoma associated with chronic cystic mastitis. It seems obvious to me why this difference occurs. Those who recognize an entity "lobular carcinoma-in-situ" may find malignancy quite frequently in chronic cystic mastitis and vice versa.

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* A section of a projected textbook or atlas of surgical pathology; Edited with comment by Milton Kannerstein, M.D.

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Duct Papilloma of the Breast

. . . Solitary large papillomas of the breast are rather rare (Fig. 2). Diffuse distribution of intraductal papillomas throughout the breast is common. The writer observed a patient who complained of nipple bleeding. The bleeding occurred only when the ten o'clock area was compressed. The surgeon carefully excised this area and a duct papilloma was demonstrated. The patient returned several months later with the same complaint. A subsequent wide resection of the breast disclosed widely distributed duct papillomatosis . . .

. . . As described above, papillomata proper of the ducts are benign new growths. However, it is the proliferative process of duct epithelium which is seen simultaneously that is important because it is this which undergoes transformation into duct carcinoma. Unfortunately such an occurrence is by no means rare, and one has to be extremely careful in dealing with instances of bleeding nipple. It may be a most difficult problem for pathologists to tell by frozen section during surgery whether or not duct cell changes are benign or malignant. This is particularly so because it is impossible to examine the entire tissue by frozen sections. It is always a possibility that one part of the breast tissue may show early microscopic carcinomatous change, where no grossly visible nodules can be seen (Fig. 3).

In order to emphasize this point a case will be described. During surgery on a patient with a bleeding nipple the writer was called to the operating room and in the removed tissue found a few small intraductal papillomata without evidence of malignancy. It was suggested, however, to the surgeon that he remove more breast tissue around the excised area. The second specimen appeared grossly to be merely fat and so no further frozen section was done. It was the latter fat tissue that proved on paraffin sections to be infiltrated by carcinoma

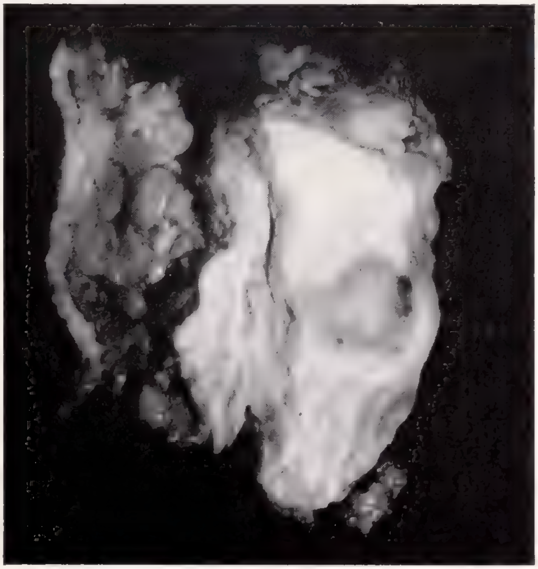


FIG. 1: An ill-defined gray nodule found within the markedly fibrotic tissue of the breast indicating infiltrating carcinoma.

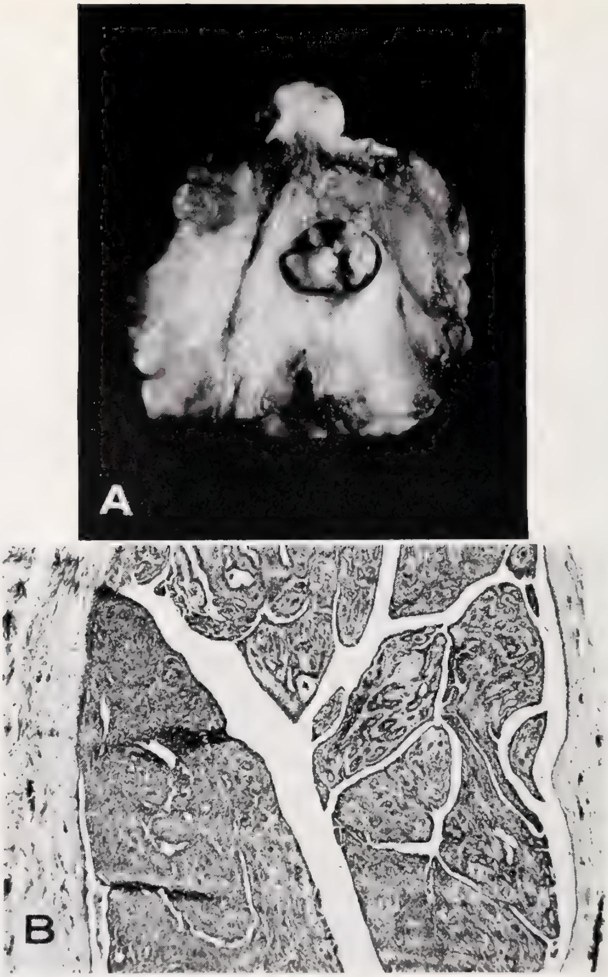


Fig. 2a: Large intraductal papilloma of the breast located near the nipple. b: Microscopic appearance of the lesion.

cells. Subsequently a radically resected specimen revealed a few more intraductal papillomata and marked proliferation of duct epithelium. It was the latter lesion that produced an infiltrating carcinoma. The papillomata were benign . . .

. . . There are cases where the proliferation of duct epithelium is rather diffuse and widely scattered, and the duct cell changes are advanced as a reason for classifying them as malignant . . .

. . . A middle-aged patient was found on operation to have duct papillomata and also extreme proliferation of duct epithelium. No further resection was carried out. During the three years following the initial operation tissue was removed on two more occasions because of ill-defined palpable masses. Identical histologic changes were disclosed. In the fourth year from the first operation,

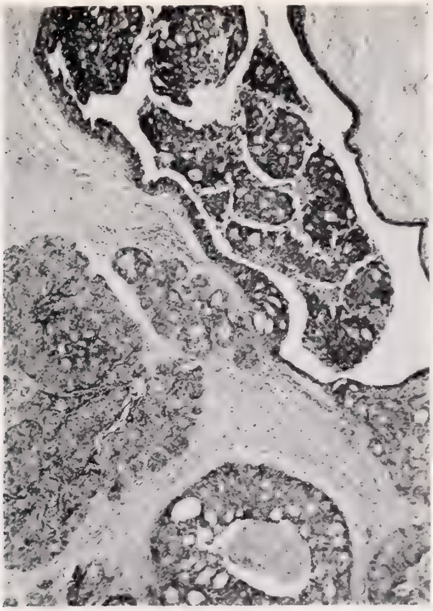


FIG. 3: Early malignant transformation in extreme proliferation of duct cells with multiple small intraductal papillomas.

a fourth operation revealed duct cell carcinoma. The radically resected specimen showed infiltrating carcinoma with axillary lymph node involvement.

In analyzing this case the following points should be emphasized. The very first specimen, although it disclosed no carcinoma, contained marked epithelial proliferation and it is quite possible that the rest of the breast tissue had similar lesions. It is also quite possible that these remaining lesions may have undergone transformation into carcinoma over a period of years, or that some may have already been malignant.

If a simple mastectomy had been performed at that time the later unfortunate outcome might have been avoided. Because of the often diffuse nature of the proliferation of duct cells the examination of a small portion of tissue does not prove that malignancy does not exist elsewhere. It is for this reason that the writer would like always to recommend a simple mastectomy in such cases. . . .

Adenosarcoma, or Fibroadenoma with Sarcomatous Transformation

. . . The effect of pregnancy on a fibroadenoma is illustrated by the following cases: A 26-year-old woman, three months pregnant, became aware of a small mass in her breast. During the next ten days it increased rapidly in size and was removed. The tumor was well encapsulated but a secondary nodule was found outside the capsule. The cut surface was homogeneously gray-white and cellular-appearing. There was no gross evidence of the usual fibroadenomatous structure. Microscopy disclosed an extremely cellular sarcomatous struc-

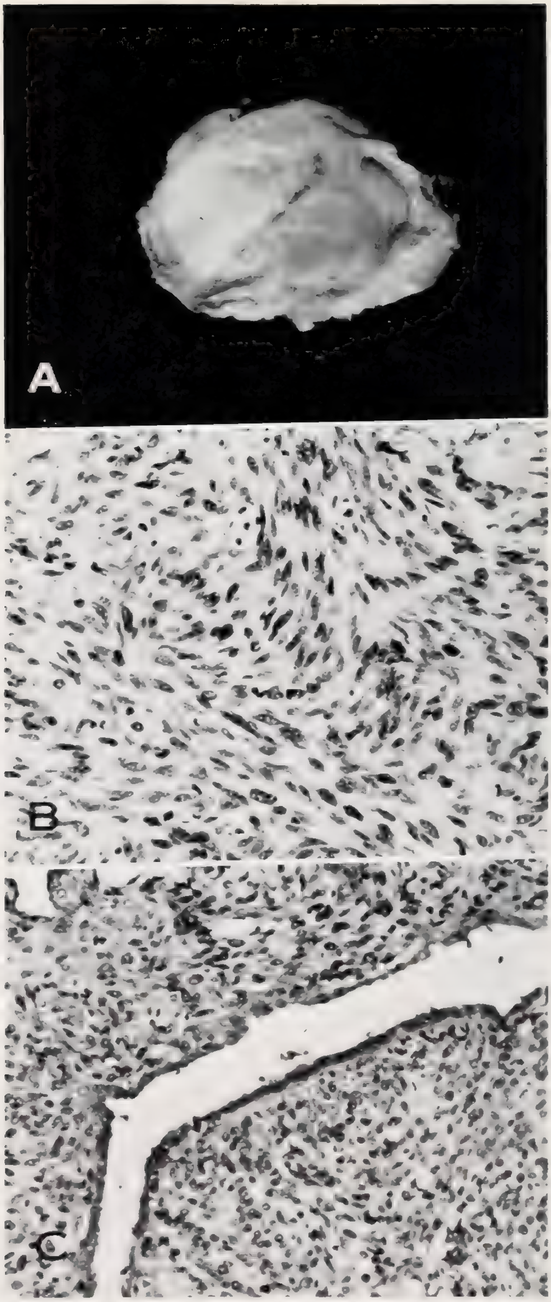


FIG. 4a: Encapsulated mass removed from breast of 26 year-old pregnant woman. b: Sarcomatous microscopic appearance of most of tumor. c: Residual fibroadenomatous area.

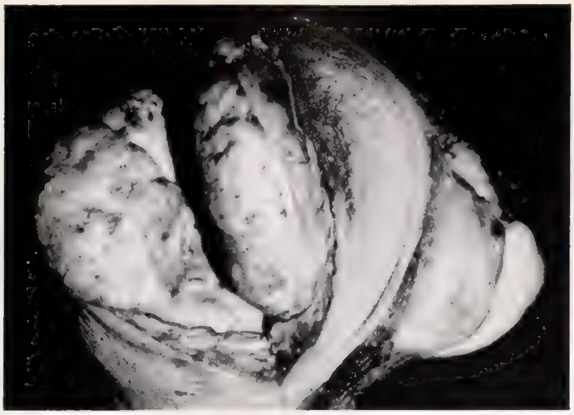


FIG. 5: Mass removed from breast of 35 year-old pregnant woman showing malignant transformation of a fibroadenoma.

ture (Figs. 4a, b, c). Scattered adenomatous elements were still present. The second case was that of a 35-year-old woman who had had a palpable nodule in her breast for at least three years. After she became pregnant the mass grew rapidly. On removal it was found to be the size of a lemon (Fig. 5), and a small accessory nodule was present.

Other Types of Carcinoma of the Breast

If one tries to make a microscopic classification of breast carcinomas, as the older pathologists used to do, there will be several more types that can be described. This serves no purpose in understanding breast carcinoma. I am of the opinion that any tumor classification should be simple. I, myself, prefer a classification based upon the gross specimen.

For instance, even if one finds an area of adenocarcinoma microscopically in a tumor that has the gross features of a scirrhous carcinoma, one should classify it as a scirrhous carcinoma. My reason for this is that, as is well known, a carcinoma of the scirrhous type may show a variety of microscopic appearances. Fig. 6 illustrates this point. In this tumor, the size of a cherry and grossly of the scirrhous type, a single section showed four different appearances-scirrhous, adeno-, medullary and duct carcinoma (Figs. 6a, b, c, d).

This is an extreme instance, but there are many similar cases. In a strict sense, there is no carcinoma which consists of one type of histologic structure. Even when a carcinoma is predominantly adenocarcinomatous, if it has a grossly scirrhous appearance, I see no objection to classifying it as scirrhous. . . .

Carcinoma during Pregnancy

. . . A microscopic picture seen in pregnancy, particularly late in pregnancy, differs from that of ordinary carcinoma, assuming a "clear-cell" appearance, because of the presence of glycogen, reminiscent of hypernephroma (Fig. 7).

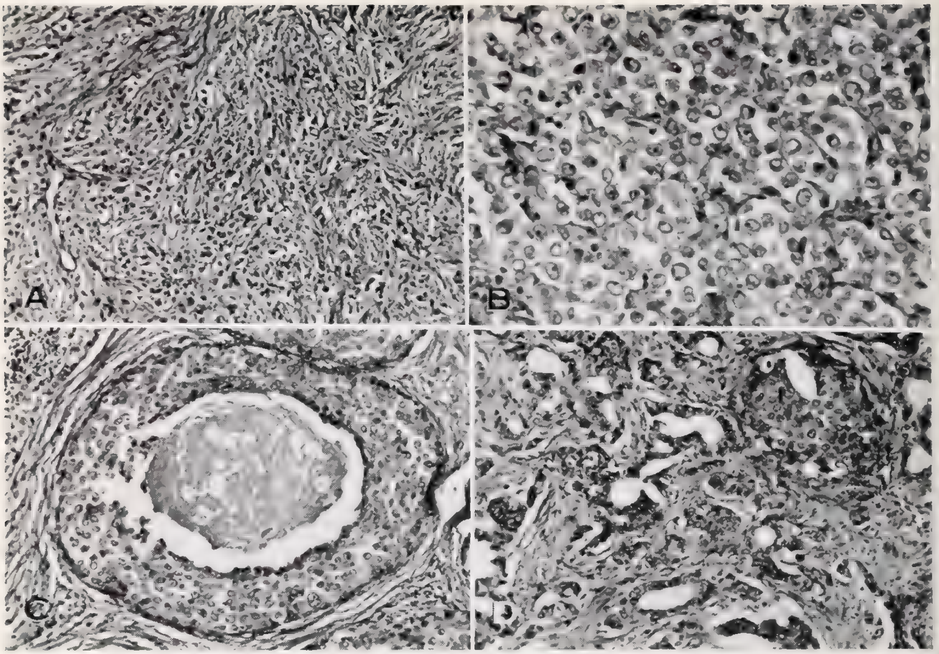


Fig. 6: A small grossly scirrhous carcinoma, the size of a cherry. On microscopic section the four different types of carcinoma found on section. a. Scirrhous; b. Medullary; c. Ductal; d. Adenocarcinoma type.

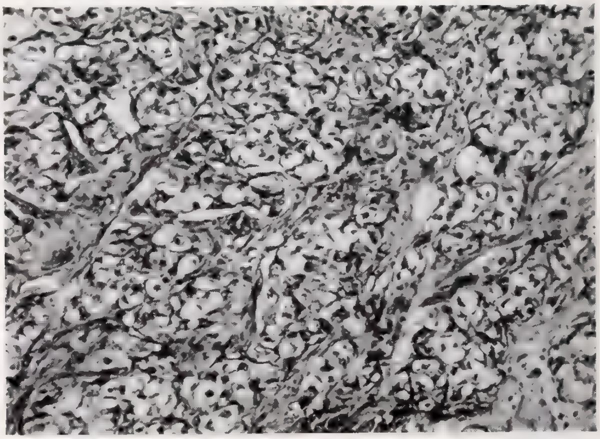


Fig. 7: Carcinoma found late in pregnancy showing "clear cell" appearance.

The Problem of Impalpable Breast Tumors in the Presence of Axillary Lymph Node Metastasis

. . . A word of caution is in order. The presence of carcinoma in axillary nodes in the absence of a palpable breast mass does not necessarily mean breast carcinoma. A careful search for carcinoma primary in other sites should be carried out in these cases. It is particularly important to rule out the possibility of an amelanotic melanoma which may simulate the anaplastic medullary type of breast carcinoma. Carcinoma of the lung is a source of axillary metastases. The author has observed the unusual occurrence of axillary metastasis from carcinomas of the thyroid and gall bladder. There is also the case of axillary metastasis from carcinoma of the contralateral breast.

It may be added that the presence of metastases in multiple axillary lymph nodes favors a mammary origin, whereas a more distant origin is likely to be represented by a single axillary node.

Cystic Carcinoma of the Breast (Cystic Degeneration of Carcinoma)

It is well known that a tumor, benign or malignant, may undergo cystic degeneration. Carcinoma of the breast is no exception. Infrequently it may be transformed into a cystic tumor. Inflammation may play an important role in producing further cystic changes. In an extreme case, the cyst lining may be smooth and be mistaken for a simple cyst. The writer observed a case in which the cyst lining was almost completely smooth with very small papillary excrescences in one area. However, the cyst contained bloody fluid different from that of an ordinary breast cyst.

In most cases of cystic carcinomas of the breast one finds an irregularly granular cyst lining. An inflammatory process occurring within the cystic carcinoma occasionally makes microscopic diagnosis quite difficult. In a frozen section only a few isolated carcinoma cells may be found scattered in the inflamed areas. It seems to me important to emphasize the existence of cystic carcinoma which simulates an ordinary breast cyst. It is common practice for surgeons to aspirate cysts of the breast and avoid excision. I am of the opinion that if aspirated fluid is bloody the cyst should be removed surgically without delay (Figs. 8, 9).

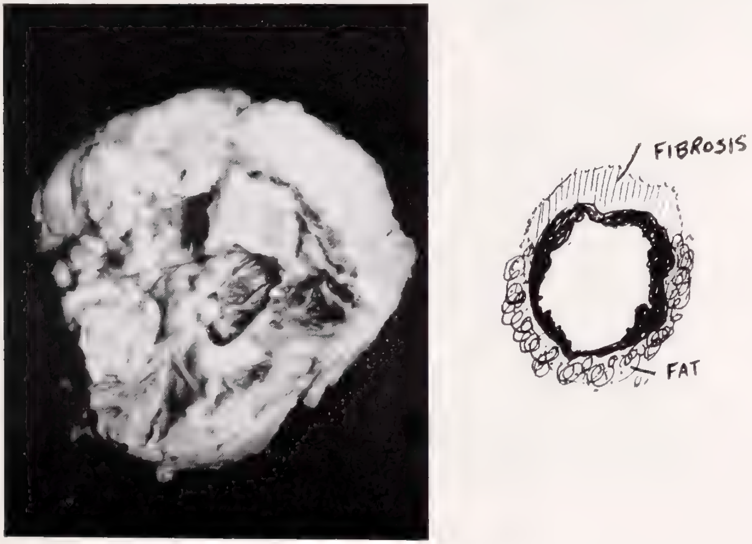


FIG. 8: Cystic degeneration of breast carcinoma. Note smooth area of lining.

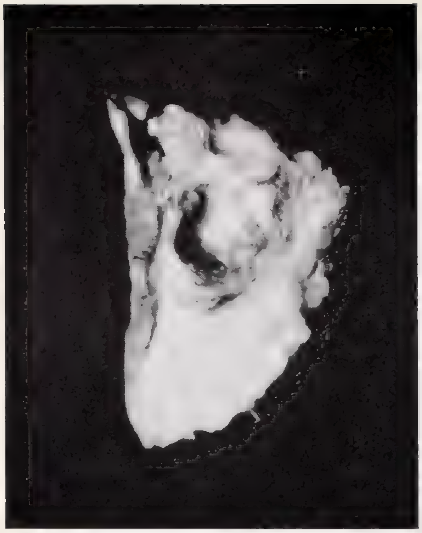


FIG. 9: Cystic carcinoma of male breast. Note smooth cyst lining in places.

There is a type of cystic carcinoma that differs from those discussed above, namely true papillary cystadenocarcinoma. The cyst is formed, not by a degenerative process but by continuous secretion. This is interpreted as a malignant transformation of a duct papilloma with excessive secretion. If this is located near the nipple, the compression may cause nipple hemorrhage. The following case illustrates this.

A 37-year-old female had a mass under the nipple. It was first felt a year before and had increased rapidly in size during the three months before operation. Pressure expelled fluid from the nipple. It collapsed after aspiration, but refilled within three days. The excised breast tissue disclosed a cyst, the size of a small lemon. Its inner surface was smooth with the exception of a few polypoid nodules in areas. These were carcinomatous. (Fig. 10)

Paget's Disease

So-called Paget's Disease of the breast is actually a malignant condition of the nipple and the underlying ducts with chronic inflammation, of many years duration. There are so many apparent variations of this condition seen as to cause confusion about its nature. This variation seems to me to represent merely different developmental stages. From cases observed by the writer the disease may be divided into the following three groups:

1) The epidermis alone shows so-called Paget cells scattered intraepidermally (Fig. 11)

2) The Paget cells can be found in the nipple epidermis and the epithelium of the nipple ducts shows early malignant changes.

3) The nipple is replaced by infiltrating carcinoma. Beneath the nipple is infiltrating scirrhous carcinoma. The corium of the nipple is also infiltrated by carcinoma cells. The periphery of the nipple epidermis still contains scattered Paget cells. (Fig. 12)

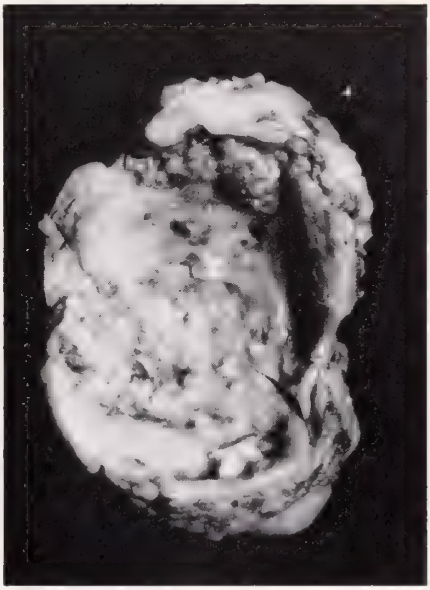
This classification seems to me to bear clinical significance. These groups can be interpreted as stages in development. In groups one and two to it is sufficient to resect only the nipple deeply; group three requires a radical mastectomy.

Tumors Originating in Accessory Breasts

Accessory breast tissue may develop various tumors such as fibroadenoma or carcinoma. Therefore these tumors may occur along the so-called breast line. The writer has observed a case of typical fibroadenoma from the abdominal wall (Fig. 13).

The most common site is the axillary region. When a carcinoma occurs in this

FIG. 10: Papillary cystadenocarcinoma of breast.



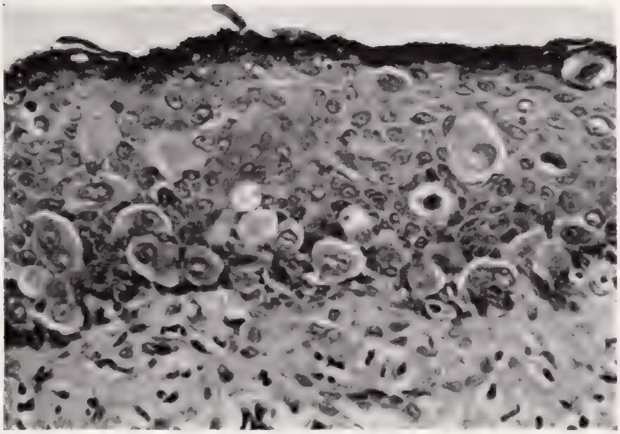


FIG. 11: Paget's disease of the nipple.

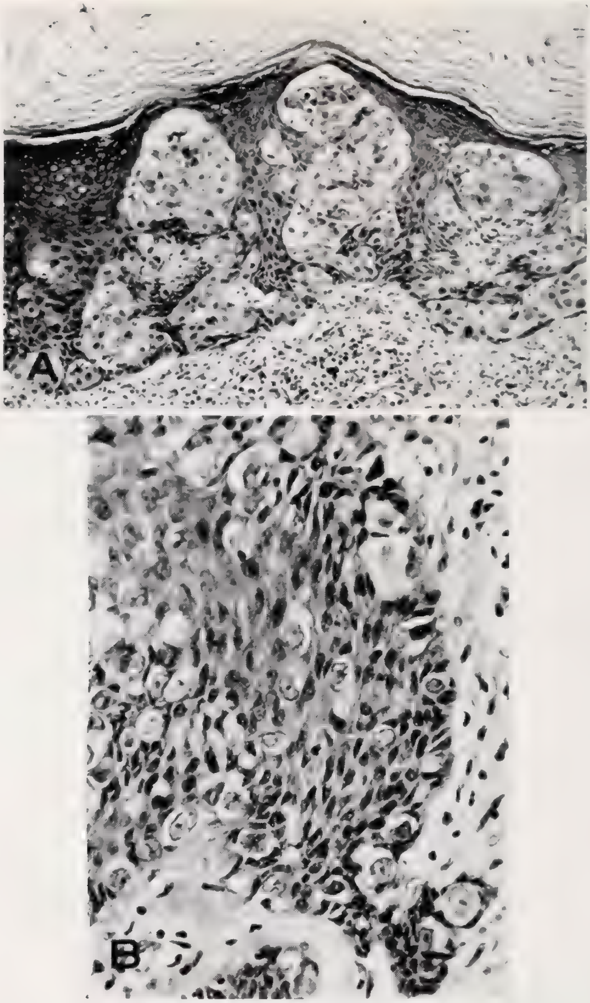


FIG. 12a: Nipple infiltrated by carcinoma cells in case with an underlying scirrhous carcinoma. b: Paget cells at periphery of lesion seen in a.

region it may be difficult to differentiate one arising in accessory breast tissue or metastatic to lymph nodes from a carcinoma in the breast proper or elsewhere. The presence of normal breast tissue around the carcinomatous mass is the only means of establishing its origin in accessory breast.

A case illustrates this point. All of four nodules found in the axilla were replaced by carcinoma. The largest proved to be the primary carcinoma because surrounding the tumor normal breast tissue was found. No trace of carcinoma was disclosed within the breast proper.

If it is definitely proven that the carcinoma is of accessory breast origin it may not be necessary to do a radical mastectomy. It is, however, by no means easy to confirm accessory breast origin on frozen section.

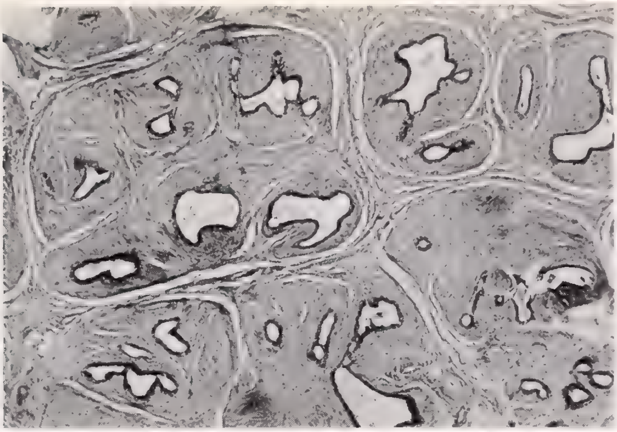


FIG. 13: Fibroadenoma removed from abdominal wall.

Difficulties in the Diagnosis of Breast Carcinoma after Radiotherapy

Radiation treatment of breast carcinoma may be remarkably effective in certain instances. Even though the tumor may have been originally quite large, there may be no residual macroscopic evidence of tumor. On close examination the breast may show advanced, diffuse fibrosis or isolated small fibrous nodules. These on cross section may have a scirrhous character. On microscopic examination isolated carcinoma cells may be found in lymphatics but even these may be few. In fact, the removed breast tissue may show no trace of carcinoma, although axillary lymph nodes still show metastatic tumor.

Comments

MILTON KANNERSTEIN, M.D.

In reviewing the extant unpublished writings and notes of Dr. Otani, the committee could only experience profound regret that in many areas where his oral teachings had been most illuminating and useful to us in our own practice, there were no written statements. In one instance, however, there was a fairly full recording of the principles of diagnosis and of his experience over many years, and that was in relation to the pathology of the breast. This was virtually in the form of a chapter or section of a possible manual, or, in combination with his usual magnificent illustrations, an atlas, of surgical pathology. It also expresses the concepts and criteria that he taught residents and those who took his course in surgical pathology under the auspices of the Post-Graduate School of Medicine of Columbia University. The date of this manuscript is believed to be approximately the early 1950's, and no other writings that may have represented developments or possible additions to his observations or modifications in his interpretations came to light.

Much of the descriptive matter might seem elementary and obvious to practicing pathologists today, but when those observations were first stated, even that category of specialist had much to learn from them.

Furthermore, these teachings were, as indicated above, directed particularly to those in a developmental stage of their careers. In 1970 residents and surgeons can still profit from these basic, precise, starkly stated precepts.

In the more speculative portions there are sections where the present predominant point of view or theoretical consensus, appears opposed to Dr. Otani's analyses. Some of the differences are more apparent than real. Moreover, it is also important to note that with respect to some of the concepts there is taking place a pendular change and one finds correlations and hypotheses being put forth recently, often arrived at by apparently more sophisticated methods—satistical and technical—but coming very close to his ideas. This, again, would illustrate his rare talents—that capacity for approaching the truth by using his powers of observation, of visual perception, which he did not permit to become obscured by preconceptions, combined with his apparently inherent need for the least complex, most spare and direct explanation. These were applied, as always with him, to a limited number of carefully selected, minutely scrutinized, and personally followed cases in arriving at a generality.

Certain parts of this subject are reproduced in the preceding pages for their own merit, and to illustrate the perspective indicated above. Dr. Otani rejected the concept of lobular carcinoma-in-situ but clearly recognized the association of carcinoma with histologically benign diffuse and scattered duct cell proliferation and recommended simple mastectomy when this proliferation was seen. To him it was a hallmark of undectable early carcinoma or carcinoma to be anticipated.

He arrived at much the same point of view with respect to Paget's disease of the nipple. He regarded the epidermal process not as an extension of underlying duct carcinoma but rather as a separate and often prior response to the same stimulus that produced the duct cell carcinoma, and affirmed in that sense their association. After many years in which Paget's disease of the nipple, as well as extramammary Paget's disease, was regarded as a continuation of duct cell carcinoma, a number of authors have presented a differing concept of pathogenesis virtually identical with that of Dr. Otani.

Trabeculated Adenoma of the Thyroid Gland and Its Malignant Transformation

SADAO OTANI, M.D.

Although the classification of thyroid tumors has been greatly simplified in the present era, it is far from satisfactory. A peculiar term, for example, "Hürthle cell tumor," which is unquestionably deficient in preciseness, if not meaningless, is still in current use. In our opinion this tumor is identical with the "proliferating struma of Langhans" which has been well known in the German literature (1). Haagensen (2), from Ewing's laboratory, designated this tumor as "Hürthle cell tumor" and others followed his lead. In recent years this term seems to have superseded the previous name.

Willis (3) in his recent book on tumors expressed his unwillingness to accept this histogenesis, although he continued to refer to this type of neoplasm as "so-called Hürthle cell tumor."

One type of benign adenomatous tumor of the thyroid, with liver-like histologic structure, has been referred to by Wegelin in the German literature as "nodular parenchymatous trabeculated struma." It was Masson who simplified this to be "trabeculated adenoma."

After examining a considerable number of tumors designated either as "proliferating struma of Langhans" (4), or "trabeculated adenoma" we fail to find specific structural differences between them. Therefore, the term "trabeculated adenoma, benign or malignant" has been adopted in our institution, and indeed has been in use for the past 20 years.

We have systematically investigated the identity of the trabeculated adenoma and also considered its relationship to so-called "Hürthle cell tumors" and the question of their histogenesis. At the same time we strive to attain a simple classification of thyroid tumors.

The specificity of this tumor, as described by Wegelin and by Masson, is in our opinion beyond doubt. Its gross appearance is rather characteristic. It is generally well encapsulated, and its cut surface appears pale gray-white, smooth, without gross evidence of colloid. It obviously contains little connective tissue, and the presence of fibrous white or yellowish areas can be demonstrated to be secondary degenerative changes.

On microscopic examination its structure is even more characteristic. It is composed of cell columns which are separated by delicate capillaries, resulting in a liver-like appearance. Variations of tumor cell arrangement, however, are noted in individual cases.

Essentially, this tumor belongs in the benign category. Nevertheless, there

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From the Department of Pathology, Mount Sinai School of Medicine of The City University of New York, N.Y. 10029; Unpublished notes; Edited with Comment by Irving M. Ratner, M.D., Department of Pathology, Albert Einstein College of Medicine, New York, N.Y. 10461.

are definite reasons why, in certain cases, contrary to the opinion of Wegelin and Masson, tumors of this type should be regarded as potentially malignant.

Although the tumor may be small and well encapsulated, it often shows areas of cell irregularity and mitotic figures. In one case, for example, many mitoses were found; and in another, conspicuous cell atypism was noted, although mitoses were few. While in those cases a definite designation of carcinoma could not be arrived at, nevertheless the features mentioned should be interpreted as early malignant changes. In other cases, in addition to the criteria of early malignant change described above there was definite vein invasion, and we consider this an evidence of malignancy.

The process of conversion of a benign trabeculated adenoma into a malignant tumor is supported by cases we have studied, where in the midst of a large invasive anaplastic carcinoma one finds areas of typical, benign-appearing trabeculated adenoma. If one pursues in detail the history of this type of case, one will discover that the patient states that a mass existed in the thyroid region for many years and then only recently began to increase rapidly in size. This supports the interpretation of the pathologic findings.

As regards the term "Hürthle cell tumor" so widely used in the English language literature in recent years, there are definite reasons for its abandonment. Hürthle described peculiar cells between the acini of the thyroid gland of dogs at a time when histologic technique was not as precise as it is today. Moreover, his concern was not with neoplasia. It is accepted today that the Hürthle cell as originally conceived does not exist.

Although it is not easy to establish a definite cell origin in every new growth, in the case of the trabeculated adenoma, however, we firmly believe that the cell of origin of this tumor has been well demonstrated to be the acinar cell by Langhans.

From our own finding in cases of trabeculated adenoma we believe that it takes its origin in the acinar cell, but in the majority of cases not in normal thyroid tissue but rather from preexisting colloid adenomas, particularly of the solid type, or the so-called fetal adenoma. In a few instances the tumor appeared to develop in an exhausted hyperplastic thyroid. The idea of origin in the fetal adenoma agrees with the fact that the latter, like the trabeculated adenoma, is potentially malignant.

Summary and Conclusions

The identity of the benign trabeculated adenoma of the thyroid gland, with its liver-like structure, which has not been clearly established in the English language literature, is stressed.

The fact that the benign trabeculated adenoma may undergo malignant transformation is emphasized. As a corollary to this, reasons are pointed out for regarding at least certain instances as potentially malignant.

Evidence is presented that the tumor arises in acinar cells of preexisting adenomas, particularly solid adenomas.

The use of the term trabeculated adenoma and the abandonment of the term "Hürthle cell tumor" are urged, and the reasons for this viewpoint discussed.

Comments

IRVING, M. RATNER, M.D.

These comments are believed to date back to the early 1950's. They are included to illustrate Dr. Otani's penchant for precision in concept and description in pathology. His designation of this tumor as trabeculated (trabecular) adenoma was finally given approval as preferred terminology by the Committee on Tumor Nomenclature and Statistics of the International Union Against Cancer in 1965 (4).

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Papillary Adenomatous Tumors of Aberrant Thyroid in Cervical Lymph Nodes

SADAO OTANI, M.D.

The question of the exact nature of papillary adenomatous tumor of lateral aberrant thyroid and its relationship to coexisting tumor within the thyroid is still under discussion in the literature.

One group of authors believes in the existence of tumor of aberrant thyroid origin and disclaims a relationship between the lateral lymph node tumor and the tumor within the thyroid. According to Lahey, Hare, and Warren (1), papillary adenomatous tumor simultaneously found in the thyroid should be classified as metastases from the lymph nodes; Crile (2) not only claims that the tumor within the thyroid is a coexisting benign papillary adenoma, but even denies the possibility of metastases to the cervical lymph nodes from papillary adenocarcinoma of the thyroid.

Other recent investigators, such as King and Pemberton (3), maintain that the papillary adenomatous tumors in the cervical lymph nodes are in reality metastases from papillary adenocarcinoma found in the thyroid; they deny the possible existence of papillary adenomatous tumor originating in aberrant thyroid.

These divergent opinions include a more fundamental problem than appears on the surface. To one who believes in the existence of aberrant thyroid origin, it is sufficient to remove all cervical lymph nodes alone for the surgical treatment of this condition, while to others who disclaim aberrant thyroid origin, it is necessary to remove a lobe of thyroid as well. It is not merely of academic interest, therefore, to settle this disputed problem, for it bears an important practical significance. Occurrence of this type of tumor is rare, and none of the investigators has had a sufficient number of cases. Tumors of this type are extremely slow in development, and it requires many years of observation to justify any conclusions.

It is the purpose of this paper to describe our cases observed during the last 15 years which, we believe, may contribute to the settlement of the long disputed question.

In one case completely resected cervical lymph nodes and a resected thyroid lobe of the same side revealed papillary adenomatous tumors within the lymph nodes, but no tumor within the thyroid. There exists no question as to the origin of the tumor; one cannot deny an aberrant thyroid origin.

Unfortunately, however, most cases reported in the literature belong to the group of cases in which, at the time of resection of the involved cervical lymph

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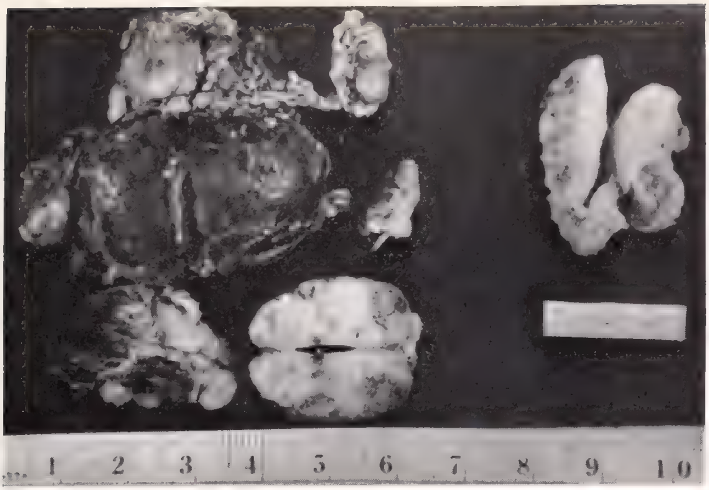

FIG. 1. Papillary carcinoma of thyroid with lymph node metastases (left).

nodes, no thyroid tissue was removed. Our two such cases showed no evidence of recurrence or metastases 10 and 11 years respectively, after the resection of lymph nodes. One inclines to assume that the thyroid has not been involved by the tumor. The evidence for it, nevertheless, is not conclusive since we are aware of the fact that this type of tumor is extremely slow in its development.

This point was challenged by the investigators who have observed cases of papillary adenomatous tumors in the cervical lymph nodes as well as in the thyroid and hastily came to the conclusion that involved cervical lymph nodes were, in reality, metastases from the papillary adenocarcinoma of the thyroid. It seems that they simply have had no cases of uninvolved thyroid in their series. Ther conclusion, however, indirectly denies a well-known fact that papillary adenomatous tumors do originate in aberrant thyroid tissue.

It is true that we, too, as pathologists, have suggested to surgeons to remove a thyroid lobe at the time of cervical lymph nodes operations and in seven such cases we always found papillary adenomatous tumor within the thyroids. However, in one instance, the tumor found in the thyroid showed such an insignificant tumor structure, one finds great difficulty in calling the thyroid tumor a primary one.

An actual site of aberrant thyroid which produces papillary adenomatous tumor has been described by many investigators; they always postulated possible embryonal tissue as a site of aberrant thyroid, but no one has definitely shown an exact site of origin.

Papillary adenomatous tumors of aberrant thyroid were always found within the lymph nodes. In some instances a large number of lymph nodes were involved and yet the tumors were only within lymph nodes.

It is well known that misplaced tissue occasionally is encountered in an otherwise normal lymph node; for instance, glandular structures resembling

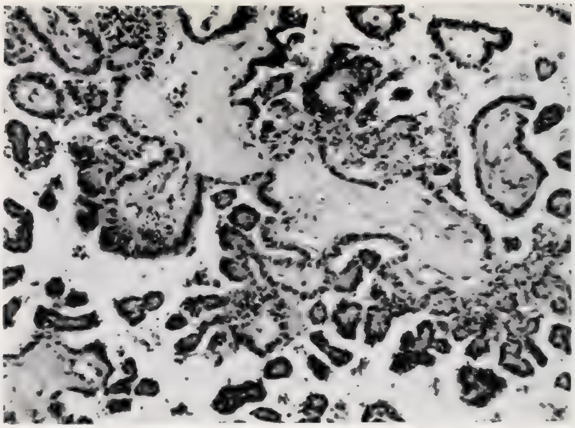

FIG. 2. Lymph node metastasis.

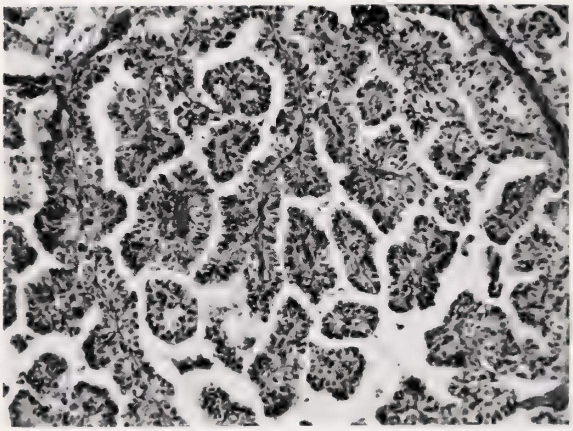

FIG. 3. Thyroid lesion.

salivary glands have repeatedly been observed in the lymph nodes of the neck. These misplaced glandular structures in lymph nodes are considered by some investigators to be an origin of "onkocytoma," and we believe in such a possibility.

With a similar idea, we suspected this aberrant thyroid tumor actually developed in the lymph nodes, which had contained misplaced thyroid tissue. We have been looking for such lymph nodes for many years, and finally we are able to collect four such instances. The finding of misplaced thyroid tissue within lymph nodes is extremely significant, for it will explain why papillary adenomatous tumors of aberrant thyroid are to be found in the lymph nodes. If one calls these tumors "papillary adenomatous tumors of aberrant thyroid of cervical lymph nodes" it is more correct anatomically than the terminology commonly used.

It seems to us that the finding of aberrant thyroid tissue in the lymph nodes has definitely established an exact site of aberrant thyroid origin. This fact gives conclusive evidence of the existence of papillary adenomatous tumors of aberrant thyroid origin.

However, there are cases in which papillary tumors are found in the lymph nodes and thyroid as well. When the tumor in the thyroid is large and only a few lymph nodes are involved, the tumor in the thyroid certainly should be interpreted as a primary tumor. This is in accordance with the opinion of other authors previously mentioned. Contrary to the opinion of Crile (2), papillary adenocarcinomas of thyroid obviously do metastasize to regional lymph nodes.

From the collected evidence through our analysis of our cases, we have arrived at the logical conclusion that papillary tumors in the cervical nodes may be either primary or metastatic.

The fact that histologic differentiation between the papillary adenomatous tumor of lateral aberrant thyroid and metastatic tumors from the thyroid often cannot be made, should be emphasized.

Summary

1. Misplaced thyroid tissue demonstrated in four different lymph nodes in three different individuals was interpreted as a possible site of aberrant thyroid tumor origin. In one case, the resected cervical lymph nodes showed multiple papillary adenomatous tumors, while the simultaneously resected thyroid lobe disclosed no tumor. In two cases, in which involved cervical lymph nodes alone (without thyroid) were removed, and were followed, 2–10 years, no development of thyroid tumor occurred. These findings give evidence that papillary adenomatous tumors do originate in aberrant thyroid tissue within cervical lymph nodes, and that they take a benign course.

2. Cases in which definite papillary adenocarcinomas are found in the thyroid, and simultaneously few lymph nodes were involved by the tumors, were interpreted as definite evidence that papillary adenocarcinomas do metastasize to regional lymph nodes.

3. The dualistic concept that papillary adenomatous tumors in the lateral lymph nodes may be either primary or secondary, brings up a considerable problem as to surgical intervention in this neoplastic disease process. It is logical to resect the thyroid lobe at the time of lymph node resection, if any tumor nodules are recognizable in the thyroid.

Comments

IRVING M. RATNER, M.D.

These observations by Dr. Otani were collated in the mid-1940's when there was deep controversy over lateral thyroid tumors (1–7). It may be difficult from the vantage of twenty-five years to appreciate the problem. However, its basis may be clarified by a review of the biology of papillary carcinoma of the thyroid.

This tumor differs markedly from most malignant tumors. The patient's presenting complaint is very often that of masses in the lateral neck with no lesion palpable in the thyroid gland either clinically or even at operation. The primary lesion may be so small that it can be identified only after multiple sections of the gland have been studied microscopically (8, 9). The microscopic pattern of cuboidal or columnar epithelial cells typically arranged as a single layer on a fibrovascular stalk with almost no atypism and very rare mitoses is hardly one to encourage a diagnosis of malignancy.

The patients are often quite young, 40 percent are below the age of forty (10). The lesions may have been present and stationary for years with even spontaneous regression and reappearance later. Not uncommonly, a tumor with many metastases may persist for years without causing death. In one series of cases of papillary carcinoma of the thyroid, only 31 of 541 patients were known to have died with and from the tumor with follow-up ranging from three to thirty years (11). In the proper evaluation of these cases, patients have to be followed for decades rather than years as with most malignant tumors.

It is noteworthy that Dr. Otani was probably the first to observe that normal thyroid follicles may be found as inclusions in cervical lymph nodes. This was, of course, a logical step in defense of the histogenesis of lateral aberrant thyroid. In their zeal to discredit the concept, some stated that normal thyroid tissue had not been found lateral to the thyroid in thousands of radical neck dissections (3, 8). Dr. Otani's observation has been confirmed by many others since (12–15).

Finally, it should be recorded that in later years Dr. Otani indicated to the writer and others that he had abandoned the concept of lateral aberrant thyroid and was convinced that these cases represented metastases to cervical lymph nodes from a primary papillary carcinoma of the thyroid.

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Syndrome of Profound Apathy (Akinetic Mutism) Secondary to Thalamic Metastasis of Unrecognized Lung Cancer

SYLVAN E. MOOLTEN, M.D.

A mass of cells in the brain stem and spinal cord (the reticular formation), long known to exist in all species, has become understood only in the last 15 years, during which time a huge literature has accumulated concerning its functions (1). The reticular formation appears to function as an enormous relay system which taps some of the energy of sensory stimuli from all parts of the body and from other parts of the brain, especially the cortex, to convert this energy into energizing stimuli to activate the central nervous system as a whole.

It has long been known that small lesions affecting a critical area in the posterior hypothalamus of the brain stem will produce prolonged somnolence (2, 3). Encephalitis lethargica (sleeping sickness) is believed to involve this portion of the brain, resulting in the peculiar disturbances in sleep and wakefulness which characterize this disease. The transitory coma of cerebral concussion is explained also by sudden interruption of function of the reticular formation, perhaps through molecular disorganization of its cells or liberation of acetylcholine (4).

In a certain sense the reticular formation may be thought of as the center of consciousness, or, at least, "wakefulness." Stimulation of the anterior portion of the reticular formation increases the activity of the entire central nervous system, producing rapid increase in its metabolism and circulation and sharp increase in functional activity. Stimulation of the posterior portion has an inhibitory effect. Many drugs which have emotional and psychotomimetic effects probably act upon the reticular formation, either to stimulate (e.g. epinephrine, amphetamines, Marsilid®, and other "psychic energizers") or to depress (tranquilizers, general anesthetics).

The following two cases appear to be examples of impaired activity of the reticular activating system produced by selective injury of the thalamus resulting in a clinical syndrome with characteristics of akinetic mutism.

Case 1: A 47-year-old electrical technician had been in good health until a few months before admission when he began to have slight difficulty in speech and slight weakness in the left arm and leg. He had been an inordinate consumer of beer (18 to 21 bottles nightly, according to his wife), yet was always thin and apparently suffered no ill-effects. During the 4 weeks before admission to the hospital the weakness of the left side of his body became somewhat more noticeable and was associated with some numbness. He was admitted to St. Peter's General Hospital, New Brunswick, where he appeared greatly emaciated and "looked like a scarecrow." X-ray film of the chest was interpreted as negative except for a questionable shadow in the left hilar region. The carotid arteriogram was reported as normal. Lumbar puncture revealed normal cerebrospinal fluid under normal pressure. Pneu-

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moencephalogram disclosed increased width of the ventricles and of the subarachnoid spaces, interpreted as "diffuse brain atrophy". The patient was discharged.

Several days later his condition deteriorated and he was therefore admitted to Middlesex General Hospital. On examination the arresting finding was the patient's unusual posture. He sat motionless and hunched forward. His face was expressionless and he was completely apathetic to his surroundings. His arms were folded, his legs were drawn up, and his eyes were closed. He was unresponsive to questions and seemed unaware of his surroundings. Neurologic examination revealed no unusual rigidity and no characteristics of the decerebrate syndrome. He was incontinent of urine and could be fed only by Levin tube. Physical findings were difficult to elicit because of his failure to cooperate but the lungs seemed to be clear. The laboratory tests showed the hemoglobin to be normal (93%); hematocrit, 46; WBC, 23,800; neutrophilic leukocytes, 89; lymphocytes, 10; VDRL negative. The urinalysis was negative. The blood pressure was 118/70. At times he seemed slightly more responsive, opening his eyes and pulling at the Levin tube. Later he would sink back into his state of profound lethargy. After a few days in the hospital he went into stupor. His skin exhibited congestive mottling. The stools became loose. Respirations became rapid and shallow, and his general condition deteriorated rapidly. Death occurred one week after admission.

Autopsy Findings: The subject appeared much older than the given age but otherwise showed no unusual features externally.

Brain: The brain was heavier than normal (1650 Gm) and swollen by moderate internal hydrocephalus. Both lateral ventricles were enlarged to about twice normal capacity. A large mass of partially softened metastatic tumor had replaced most of the left thalamus and caudate nucleus and encroached upon the third ventricle, partially blocking the aqueduct. A smaller tumor nodule was present in the posterior pole of the limbic lobe of the right cerebral hemisphere near the basal ganglion and contributed to the narrowing of the aqueduct. In the right cerebral hemisphere, about midway from occipital to frontal poles, a third rounded nodule 3.0 cm in diameter bulged upon the ependymal surface. This nodule also had undergone partial liquefaction.

Lungs: A sharply demarcated tumor mass, slightly smaller than a golf ball, was embedded in the left upper lobe near the hilus of the lung. It was friable and much of its center had undergone softening. The tumor surrounded and compressed the primary branches of the upper lobe so that most of the left upper lobe was atelectatic. Distally the lumens of the bronchi were distended with mucopurulent exudate. The tumor also compressed a large pulmonary vein and protruded into its lumen. Microscopically the tumor was identified as "oat cell carcinoma."

An enormous mass of metastatic tumor replaced most of the right adrenal gland and the upper fifth of the subjacent kidney. A minute metastasis was detected microscopically in the pancreas.

Case 2: An 84-year-old man had been apparently well until one month before admission to the hospital when he became unusually drowsy and slept most of the time. He ate little and lost considerable weight. For 2 days before admission to the hospital he slept almost continually.

On examination in the hospital he was drowsy, dehydrated, and emaciated. He appeared neglected and was very dirty. He did not respond to commands and remained sitting when asked to lie down. He did not speak and made very few spontaneous movements. Physical examination was otherwise unremarkable except for caked feces in the rectum and enlargement of the prostate. Several decubitus ulcers were present over pressure points. The blood pressure was 150/90. The clinical impression was "malnutrition, possibly the result of gastrointestinal malignancy." X-ray examination of the chest disclosed a single rounded nodule 4 cm in diameter in the right basal lung field which had the appearance of "metastatic nodule, possibly arising in a tumor of the kidney."

The laboratory findings were unrevealing, the hemoglobin, 15 Gm.%; hematocrit, 43; WBC, 13,200; neutrophiles, 64. The blood urea nitrogen was 26 mgm%; total protein, 6.4 Gm.%; albumin, 4.6; globulin 1.8. The blood sugar was 88 mgm.%. Gastric washings

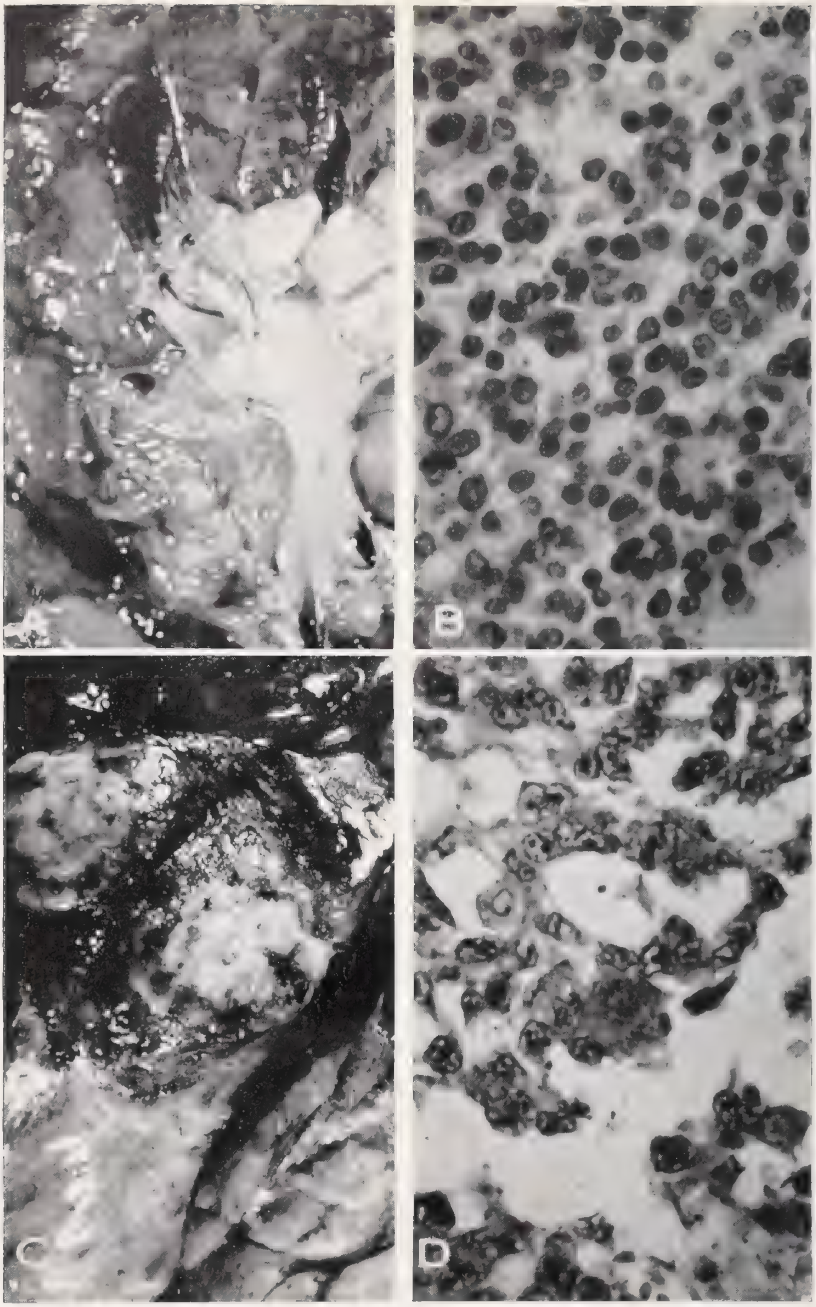

FIG. 1. A. Carcinoma of upper lobe of left lung (Case 1) showing protrusion into lumen of vein. B. Undifferentiated "oat-cell" carcinoma (Case 1). C. Parenchymal carcinoma (Alveolar cell adenocarcinoma) arising in scar tissue, upper lobe of right lung (Case 2). D. Anaplastic alveolar cell carcinoma (Case 2).

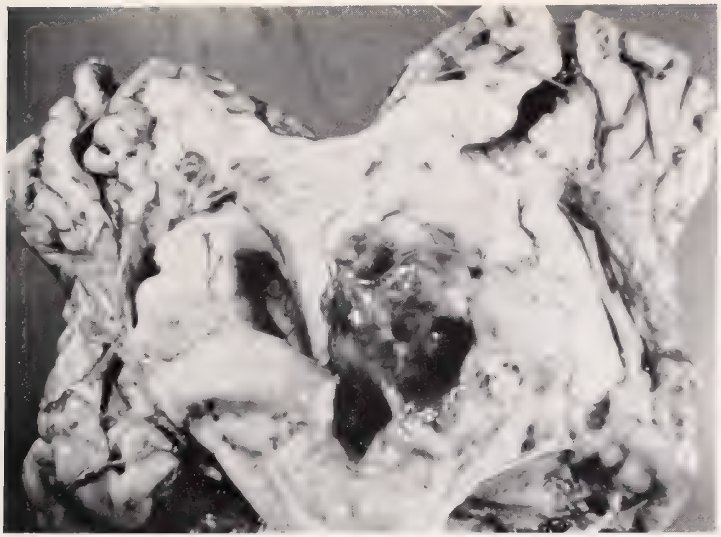

FIG. 2. Metastatic tumor, right basal ganglion (Case 2).

revealed no tumor cells in the sediment. The electrocardiogram was not remarkable. Liver function studies were negative. The sedimentation rate (Westergren) was 7 mm in 1 hour. The serum sodium was 138 mEq/1; potassium, 4.4; chlorides, 102.2; CO_2, 69.8 vol.%. The urine contained a trace of protein, many pus cells, a few RBC, and many bacteria. The stool was negative for occult blood. The alkaline phosphatase was 7.1 Bodansky units, acid phosphatase 0.6 Bodansky units.

The patient appeared to have difficulty in swallowing solids or liquids. He began to drool coffee-ground material and refused to eat. X-ray studies of the gastrointestinal tract revealed poor function of the esophagus with segmental dilatation and stasis. The stomach showed some inflexibility of the cardiac and antral portions highly suggestive of malignancy and there was considerable gastric retention at 90 minutes.

He became increasingly somnolent, and incontinent of urine. At times he seemed frightened, deeply confused, and very resistant. Later he sank into deep lethargy, staring into space. He died about 1 month after admission.

Autopsy Findings: The subject was extremely emaciated. The skin of the extremities exhibited numerous areas of purpuric hemorrhage. There was no edema, jaundice, or clubbing. The musculature was markedly wasted and the general appearance suggested marked cachexia.

Brain: The brain was easily removed and appeared uniformly shrunken, weighing 1150 Gm. The sulci seemed somewhat widened and the gyri correspondingly narrowed. The ventricles were moderately dilated. Dissection revealed a remarkable tumor mass of the right basal ganglion which had replaced most of the thalamus and striate body. It protruded sharply into the right lateral ventricle which it filled almost completely. The mass measured 3.5 x 3 cm, approximately the size of a small plum. It was friable, dark brownish red, partly necrotic and hemorrhagic. A pea-sized nodule of similar character was embedded in the right cerebral cortex. Both lateral ventricles were somewhat dilated.

Microscopically the tumor mass was composed of spindle-shaped cells of irregular contour with large vesicular nuclei showing frequent mitoses. Some of the cells had giant nuclei. Much necrosis was present. In a few areas the tumor cells were organized in papillary fashion about blood vessels. Tumor tissue filled the lumens of several small veins within the tumor.

Lungs: The right lung contained a rounded tumor nodule 4 cm. in diameter in the subpleural region of the right lower lobe. It had a greyish-brown cut surface mottled with anthracotic pigment. It was sharply circumscribed. Its histologic features suggested anaplastic alveolar cell adenocarcinoma arising in scar tissue. Extensive bronchopneumonia was present in the remainder of the lungs.

Adrenals: Both adrenals were slightly enlarged. The left adrenal contained a pea-sized whitish nodule of tumor similar to that in the lung. The other organs exhibited changes characteristic of advanced malnutrition. The liver weighed only 950 Gm.

Comment

The clinical picture presented in these two cases was dominated by the striking apathy of the patients and apparently complete lack of awareness of their surroundings. They were unresponsive to normal stimuli or to commands of the examiner, and spontaneous movements were few. Profound weight loss resulted from failure to take sufficient food. Feeding in the hospital could be accomplished only by artificial methods. The attitude assumed by both patients was reminiscent of the decorticate monkey.

In all major respects the clinical findings in both cases can be regarded as characteristic of akinetic mutism, a variety of disordered consciousness in which the patient lies speechless and motionless in bed and makes very little response to stimuli (5). He appears to be asleep, but can be aroused. His eyes may follow moving objects and deviate in response to loud noises. There are neither voluntary nor restless movements of the extremities, but there is reflex withdrawal to painful stimuli. The patient has to be fed; he does not chew but is able to swallow. He is incontinent of urine and feces. This syndrome, which is also referred to as "coma vigil," has been described with encephalitis, tumors of the third ventricle, midbrain trauma, thrombosis of the basilar artery, and Wernicke's syndrome.

The organic basis for akinetic mutism in these two patients is attributable to the destruction of a large component of the reticular activating system by metastatic cancer. In neither case was there histologic evidence of loss of neuronal elements in the cerebral cortex. The findings on pneumoencephalography in Case 1, interpreted as "diffuse brain atrophy," and the shrunken appearance of the brain at autopsy in Case 2 are therefore explained by reduced cerebral metabolic activity, hence reduced blood flow to the brain as a whole, owing to suppressed function of its reticular activating system.

The anatomical explanation for localization of cerebral metastases in the basal ganglia in both cases probably lies in the circumstance that the brain, like the adrenal glands, is in direct vascular communication with the lung through the vertebral venous plexus via the intercostal veins and veins of the pulmonary ligament. The landmark studies of Batson (6) on the vertebral vein system provide the most reasonable explanation for the frequent selective localization of metastatic lung cancer in either or both of these two organs, which are often the sole sites of metastasis from the lung. Personal observations which support this interpretation include the occasional demonstration of tumor emboli in the adrenal veins and pial veins (not arteries) in relation to such metastases. In the present case the probable route of retrograde venous metastasis to the thalamus included sequentially the straight sinus of the dura, the great vein of Galen, the internal cerebral veins, and their tributaries within the thalamus.

Summary

Akinetic mutism (coma vigil) may be the sole presenting clinical feature of thalamic metastasis of lung tumor. In two cases of this syndrome the patients became profoundly emaciated. Brain shrinkage, demonstrable clinically by pneumoencephalography or anatomically at autopsy, was explained as the result of reduced cerebral metabolic activity and consequently reduced cerebral blood flow attributable to impaired function of the reticular activating system.

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Glomic (Paraganglionic) Tissue in the Larynx and Capsule of the Thyroid Gland

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Introduction

Since the discovery by Otani of tumors of the middle ear as carotid body tumor analogues 30 years ago (1–3), the existence of these tumors has become accepted universally, although his contribution to their recognition is still widely unknown.

In the intervening years much progress has been made in various fields, such as the discovery of similar structures or neoplasms arising from glomic tissue in other parts of the body, including lung (4–7), nasal cavity (8), duodenum (9), and larynx and trachea (10, 11). Studies utilizing the application of special silver impregnation techniques (12–14), ultrastructural (15–17) and histochemical approaches (18–20), and pharmacologic methods (21, 22) have all successfully attempted to define the role of "paraganglia" as neurosecretory organs.

It is the purpose of this study to report and illustrate the occurrence of "paraganglia" encountered over the past seven years while studying serially sectioned cancerous and irradiated larynges. With the exception of a brief comment in a previous publication (23), we have not alluded to this observation. It was only when we started to concentrate on these structures in preparation of this paper, that we became aware of the fact that German investigators made similar observations also within this period (24–27), and that neoplasms arising from such laryngeal "paraganglia" have been reported since 1955 (28–30). We have also found glomic tissue in relation to the nearby thyroid gland, spread over or within its capsule.

Discussion

The anatomist Watzka, known for his many studies of the paraganglionic system, recently described minute "paraganglia" in serially sectioned larynges of adults, which were used as teaching material for medical students (24). These structures were small, paired and often multiple, measuring 0.1 to 0.3 mm, and were located in the upper and anterior third of the ventricular fold, near the superior margin of the thyroid cartilage. His pupil, Schönberger, confirmed these findings in a study of neonatal larynges, and similarly noted their intimate relationship to autonomic ganglia and to fibers of the internal branch of the superior laryngeal nerve (26).

These findings stimulated the laryngologist Kleinsasser to look for related structures in the subglottic larynx (25), where glomic neoplasms have been reported. He discovered a similar pair of slightly larger structures (0.3–0.4 mm)

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in the first neonatal larynx examined, in the space between the inferior horn of the thyroid cartilage and the cricoid cartilage. These also had a close relationship to branches of the inferior laryngeal nerve, and to the inferior laryngeal artery. He named them the inferior laryngeal glomera, and labelled those of Watzka the superior laryngeal glomera. In a second neonatal larynx studied, he described additionally an anterior laryngeal glomus, situated in the midline in front of the cricothyroid membrane. This structure is of inconstant occurrence, as it has not been encountered by subsequent observers.

A later study of 10 premature and full-term neonatal larynges by Jansen and Netty-Marbell (27) confirmed these observations, but pointed out that the upper pair was seen in only 50% of their material. The inferior pair was constant. However, several of them were situated more caudally, in the space between the cricoid cartilage and first tracheal ring.

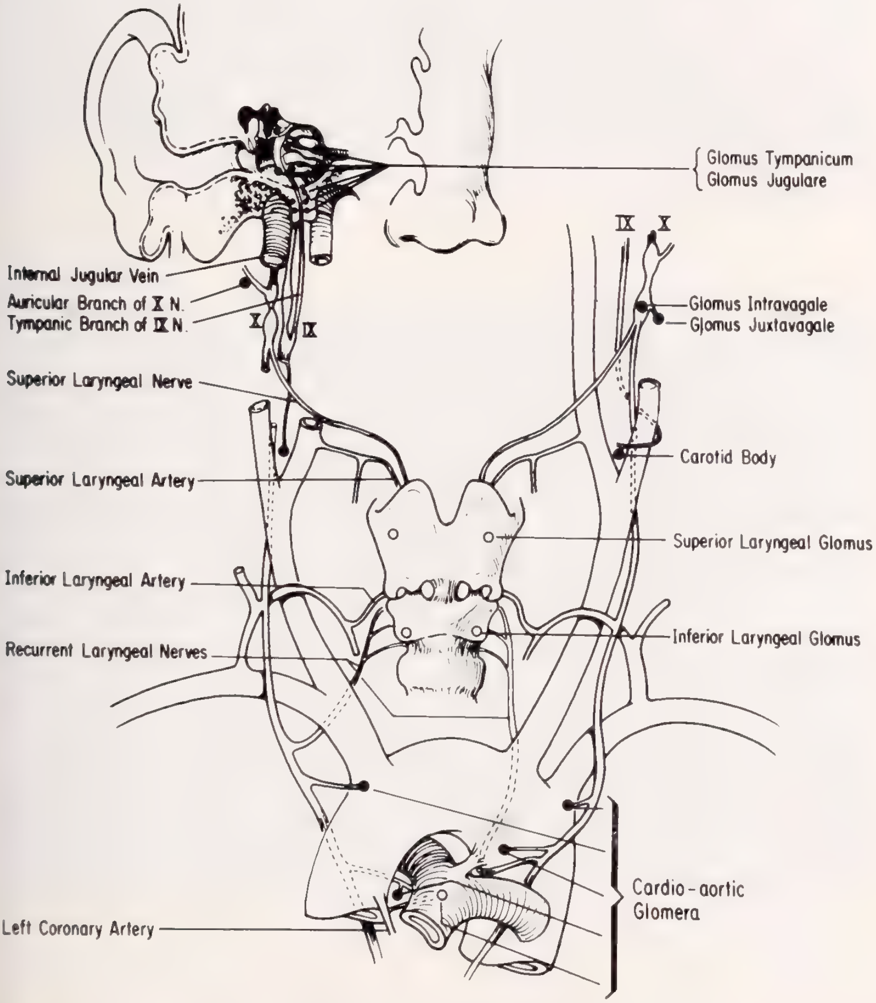
Glomus Tympanicum
Glomus Jugulare
IX
X
Internal Jugular Vein
Auricular Branch of X N.
Tympanic Branch of IX N.
X
IX
Glomus Intravagale
Glomus Juxtavagale
Superior Laryngeal Nerve
Carotid Body
Superior Laryngeal Artery
Superior Laryngeal Glomus
Inferior Laryngeal Artery
Inferior Laryngeal Glomus
Recurrent Laryngeal Nerves
Cardio-aortic Glomera
Left Coronary Artery

FIG. 1. Diagram of topography of glomic tissue.

Initially we discovered the inferior "paraganglia" by serendipity, while examining serial sections of adult cancerous larynges. On review of our material we also found superior paraganglia. The latter structure in our experience also is the smaller of the two, spherical and situated in a relatively fixed location in the upper larynx, as noted by all investigators. The inferior laryngeal glomus is slightly larger, and we have found it in the adult most often between the cricoid cartilage and first tracheal ring, rather than the higher site originally noted by Kleinsasser. In two cases there was close proximity to the thyroid gland. Its shape is more variable, and it may be spherical, band-like, or consist of scattered small aggregates within nerves and small ganglia, or close to arteries. It is also worthy of note that no radiation effect was observed in the paraganglia and that the neonatal structures are the same size as those of adults. Chromaffinity was absent in the paraganglia of the newborn fixed in Zenker's solution.

Summary

Glomic (paraganglionic) tissue occurs in the adult larynx, in the same location as described in the neonatal larynx, as two paired organs of microscopic dimensions (Glomus laryngicum superius and inferius), in relation to branches of the superior and inferior laryngeal arteries and nerves. The inferior glomus may extend to the adjacent thyroid gland. Tumors arising from these structures have been reported.

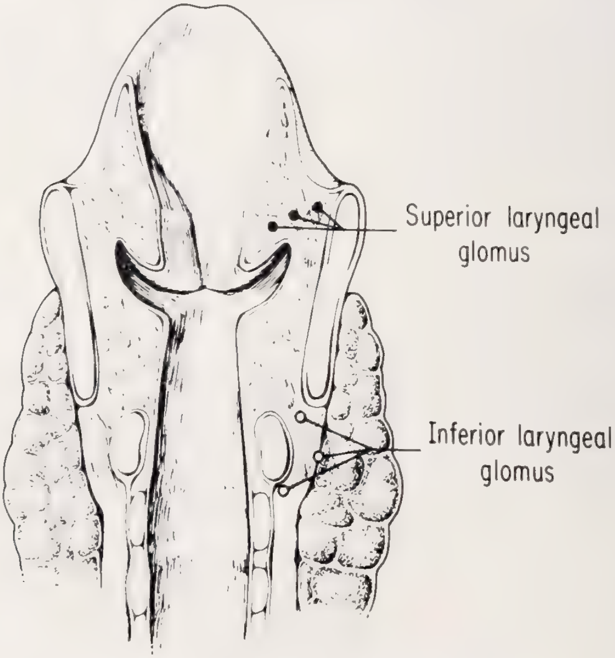

FIG. 2. Diagram of laryngeal glomera. Glomic tissue in relation to the thyroid capsule is evident. The inconstant anterior laryngeal glomus (Kleinsasser, 1964) is not included in this diagram.

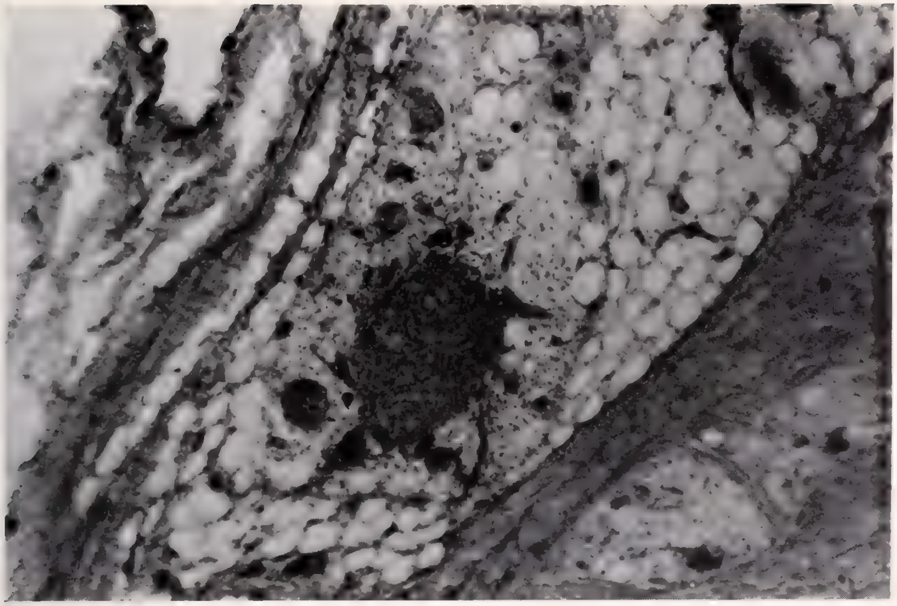

Fig. 3. Inferior laryngeal glomus (× 45).

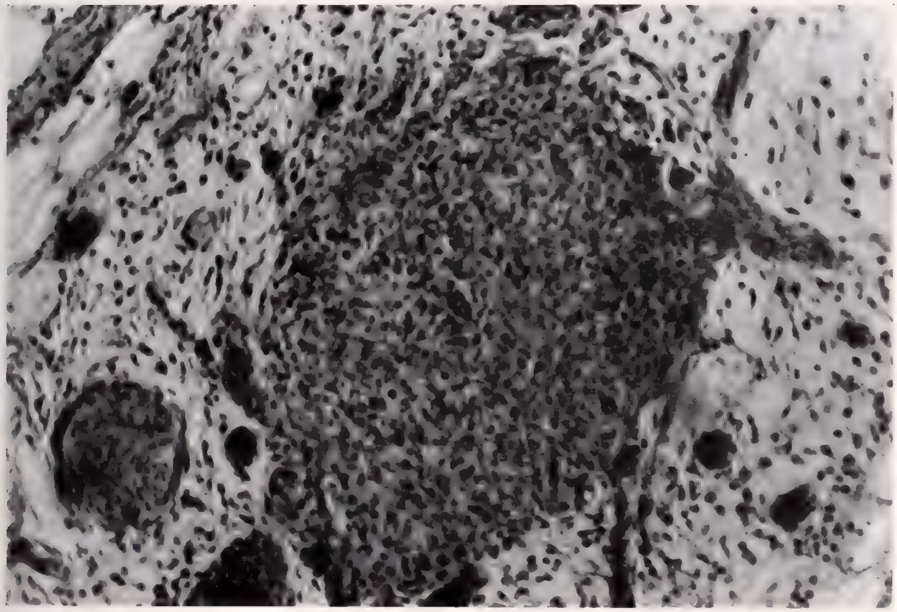

Fig. 4. Same (× 125). Note nerves at periphery.

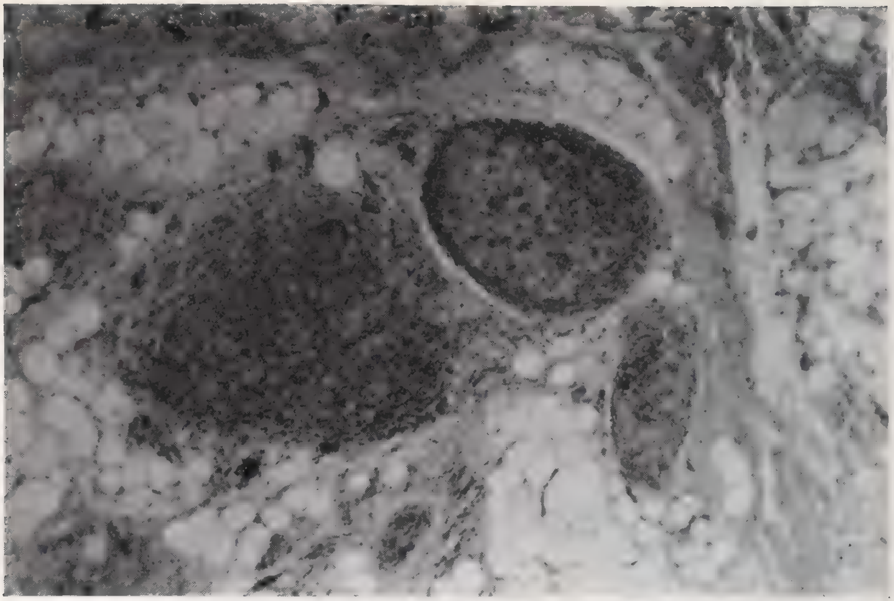

FIG. 5. Inferior laryngeal glomus with associated ganglion and nerve at right (× 45).

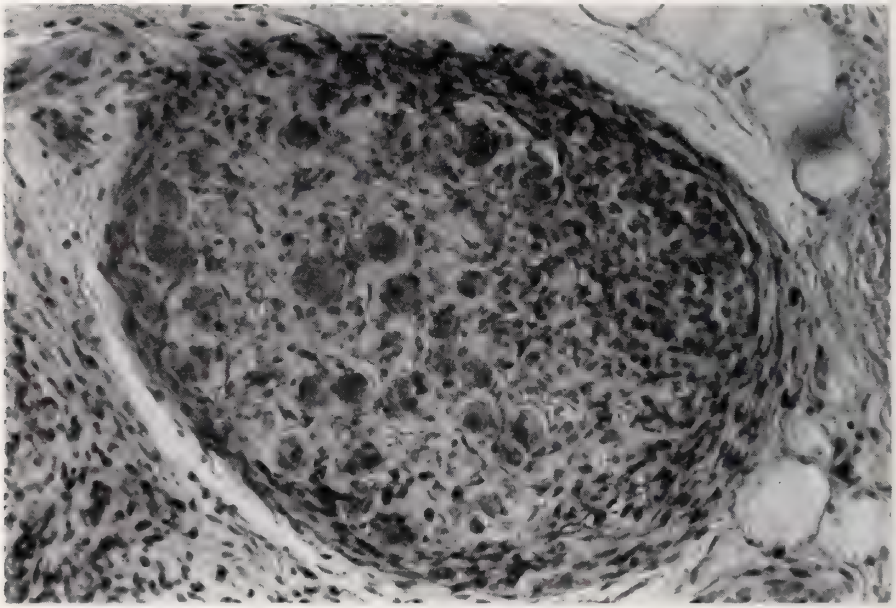

FIG. 6. Same showing glomic tissue within right upper quadrant of ganglion (× 125).

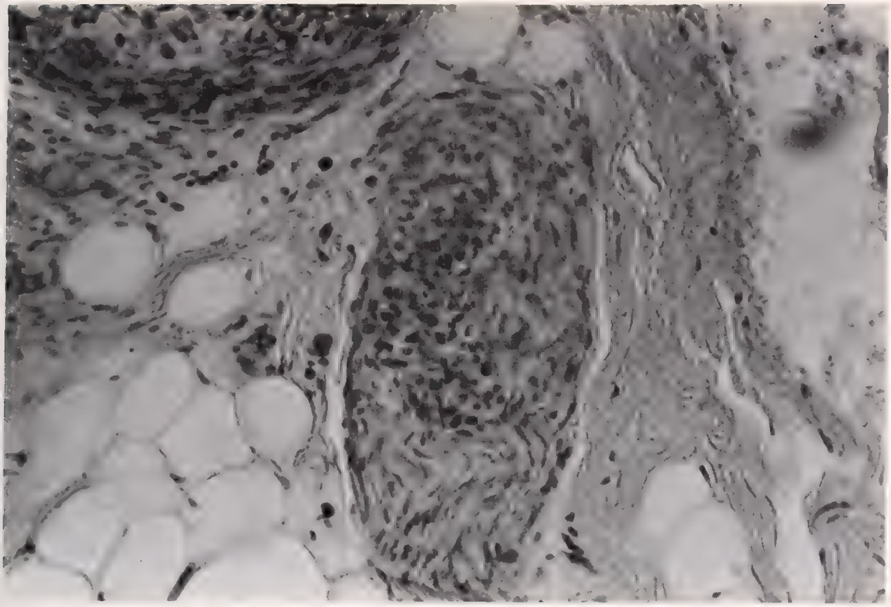

FIG. 7. Same showing glomic tissue within nerve. (× 125).

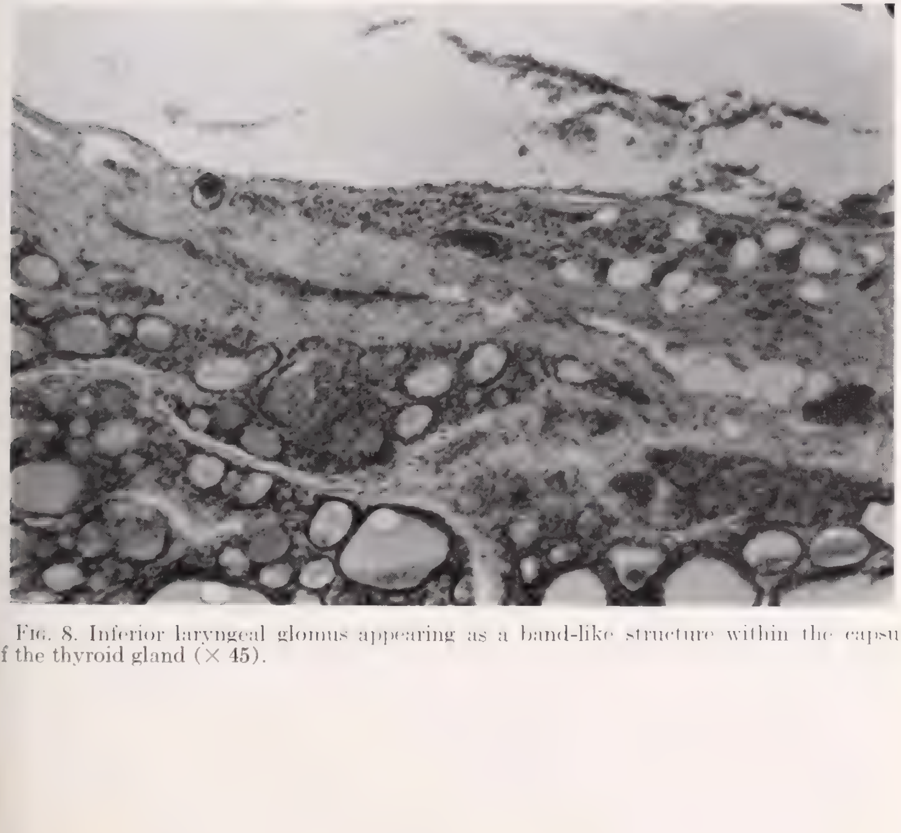

FIG. 8. Inferior laryngeal glomus appearing as a band-like structure within the capsule of the thyroid gland (× 45).

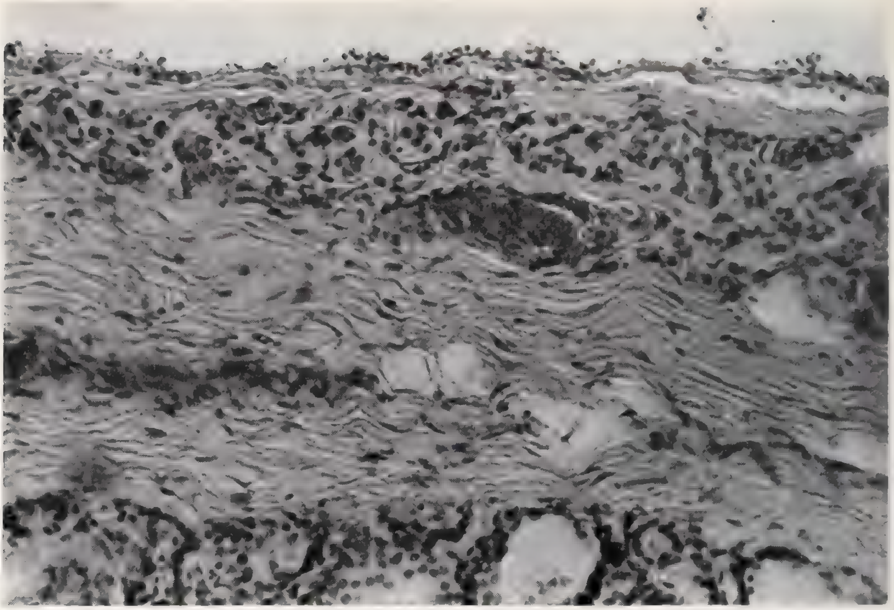

FIG. 9. Same (× 125).

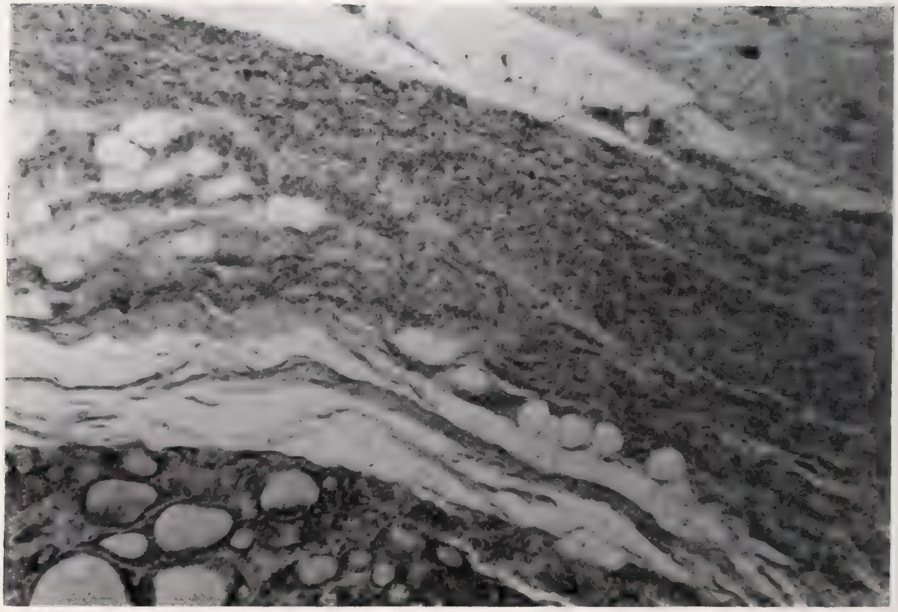

FIG. 10. Broad band of inferior laryngeal glomic tissue outside thyroid gland (× 45).

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The Analogy of Amyloid and Keratin as Suggested by X-Ray, Amino Acid, and Ultrastructural Analysis

BORIS GUEFT, M.D.

Despite recent advances in understanding the fine structure of amyloid material and its cellular relationships, discordant findings and interpretations point to a lack of correlation between immunohistochemical determinations (1–7) and chemical data such as amino acid and polysaccharide analyses (8–14). Amyloid remains unclassified by modern analytic criteria.

It is now thought that there are only three stable configurations of the polypeptide chains of proteins, namely, the alpha helix (e.g., hair keratin), the beta sheet (e.g., beta keratin and silk), and the polyproline helix (e.g., collagen).

It is the purpose of this communication to present new x-ray diffraction data and to correlate these findings with previous x-ray studies as well as electron microscopic data and amino acid analyses in order to better understand this fibrillar protein and compare its structure to a few similar materials.

Materials and Methods

Amyloid-laden liver from a case of severe amyloidosis associated with tuberculosis was cut into fragments less than 2 mm in size with a sharp knife. The fragments were crushed with moderate pressure in a porcelain mortar in distilled water (1 gram tissue to 10 ml water). The mixture was then filtered through coarse gauze and centrifuged at 3800 rpm for one hour in a Clay-Adams CT 1004 D centrifuge in swinging 25 ml tubes. The upper fluffy layer of centrifugate was removed, resuspended in distilled water and centrifuged again to a total of ten times. The final fluffy layer was checked by negative contrast electron microscopy and found to consist of typical wavy double fibrils. The material was prepared in different ways for x-ray diffraction. The best patterns were obtained by crystallizing the material for one month in a protected horizontal glass capillary tube 0.5 mm in diameter, at room temperature. At the end of this time, the tube was split with a diamond tool and the best oriented fibers were chosen under a polarizing microscope. These moist fibers were mounted on a wire loop between two sheets of moistened Formvar® (Shawinigen Products) membrane, each about 1 micron thick as judged by optical appearance. A Chesley-type micro camera (Philips Electronics Co., manufacturer), was utilized, with a 50-micron diameter lead glass tubular collimator, and a nominal specimen-to-film distance of 1.5 cm. Calibration was with calcite or sodium fluoride powder placed next to the specimen after a successful pattern of the amyloid was obtained. A nickel-filtered Cu K-alpha radiation (40 KV 18 milliamperes) was employed for 10 to 20 hours. The film was double-coated high-

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speed Kodak® Industrial emulsion, developed in Kodak x-ray developer for 8 minutes at 21°C. Measurements were made on 10x precision enlargements with superimposed precision metric scale. These were also checked against direct measurements of the negative with a metric vernier. In addition, some measurements of the sharpest lines were made from diffraction patterns on a low angle version of the Chesley camera with film-to-specimen distance of 4.14 cm.

Results

The best fiber diffraction pattern is shown in Figure 1. This has: (1) A series of fairly sharp equatorial reflections apparently corresponding to orders of a 95.8 Å (approx.) spacing. (2) A series of reflections varying from 4.71 to 2.86 Å, which in many exposures were arc-like and present mainly on the meridian. (3) A broad diffuse ring at about 10 Å, with vague spots on the equator. (4) A broad overlaid ring or halo at about 4.7 to 3 Å. Measurements of the reflections are given in Table I.

In some less-oriented specimens, the group of rings at 4.7 to 3 Å merged into a single diffuse ring with barely visible sharp superimposed meridional arcs. The equatorial reflections were always quite distinct, and the 15.6 Å reflection was consistently the strongest. No 1.5 Å reflections were present.

Discussion

This pattern (Fig. 1) is less detailed than, but similar to, the pattern described in the original x-ray diffraction studies by Shmueli, Gafni, Sohar and Ashkenazi in 1967 (15, 16) (Fig. 2a). Their interpretation is that the amyloid fibrils are aggregated laterally, that the interlayer distance is about 94 Å, and that ordered fibrous particles are present with a large repeating unit. They state that a fibrous protein of the Astbury KMEF (keratin, myosin, epidermin, fibrin) or collagen classes (Dickerson 17) can not be present, and they favor the idea of an ordered polymer of globular subunits. At the presentation of the pattern of this report in 1968 (18), my opinion was that an alpha helix also was not present (Fig. 2b), but that the pattern had a general resemblance to those of poorly oriented beta proteins (19) (Fig. 2c and d) and had a degree of complexity and some reflections like those of feather keratin (20) (Fig. 2e).

TABLE I

Measurements of the Reflections of the Pattern in Figure 1

Equatorial Reflections				Meridional Reflections	
Io	d obs. (A)	N	d calc (Å)	Io	d obs. (Å)
Strong	23.5	4	23.35	Strong	4.71
Strong	15.6	6	15.97	Strong	4.33
Medium	12.4	8	11.93	Medium	4.08
Weak	9.35	10	9.58	Weak	3.79
Weak	8.26	12	7.99	Moderately Weak	3.38
				Very Weak	2.86

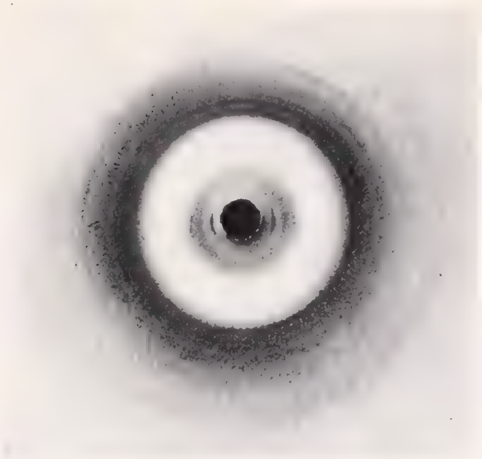

FIG. 1. X-ray diffraction pattern of amyloid fiber. Chesley Microdiffraction Camera; Cu Kα radiation, Ni filter, 45 KV 18 milliamperes 15 hours. Specimen-film distance 1.5 cm. Collimator: Lead glass Capillary 50 micron diameter. Fiber axis upright.

This compound has a controversial structure and is thought by some to have a beta sheet structure and by others to have even a double helix made up of tiny crystals each made up of beta type sheets. (v.i.). The striking resemblance of the amyloid pattern to the silk-like egg stalk beta protein of the insect Chrysopa flava (21) was also pointed out (Fig. 2f).

Eanes and Glenner (22) have also studied the x-ray diffraction of oriented amyloid fibers. They concluded that the sharp 4.75 Å ring they obtained as well as a 4.3 Å halo and a 9.8 Å ring all correspond to a beta configuration (pleated sheet). On the basis of pattern variations with x-ray beam position and with pressure, they specified that the cross-beta pleated sheet is present, with ribbon-like micelles running transversely in the fibrils. They also noted the resemblance of the pattern to that of Chrysopa protein and pointed out that this often has a cross-beta arrangement of polypeptide chains. They apparently were unaware of the faint equatorial reflections present in Figure 3 of their paper and of Shmueli's detailed pattern of 1967 (15, 16).

It has been pointed out that the electron microscope images of certain keratins and amyloid have strong resemblances (23, 24). It is therefore worthwhile to attempt to correlate the known physical and chemical properties of these two proteins in order to better understand the results of the x-ray diffraction.

Electron microscopic images of amyloid have shown 96 Å wide fibrils made up of two filaments that twist about every 1000 Å. A 40 Å periodic cross striation is often seen (25, 26, 27). Trypsin digestion appears to remove a coating from the filaments (24). Feather keratin and alpha keratin (wool) both have fibrils whose width is close to that of amyloid with possibly two intertwined filaments with a period of 1500 Å. Fine cross striations are also seen (28–30). Shmueli et al.'s suggestion that ordered fibrous particles are present along the amyloid fibrils certainly agrees with the electron microscope appear-

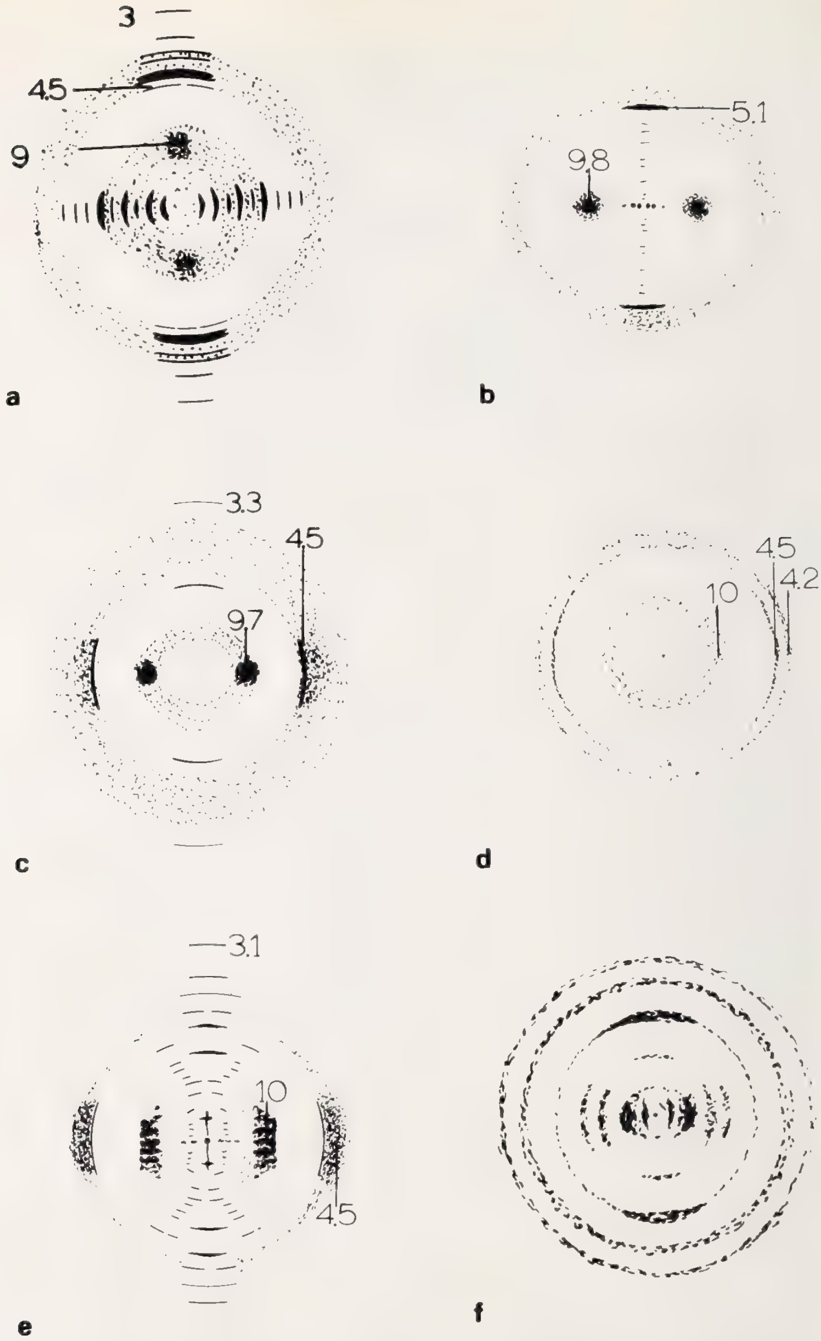

Fig. 2. (a) Amyloid: Sketch based on Shmueli, Gafni, Sohar, and Ashkenazi's x-ray diffraction pattern of purified amyloid (16). (b) Sketch of alpha keratin diffraction, based on Mercer (19) and Dickerson (17). Fiber axes all upright. (c) Beta keratin, as in b. (d) Unoriented Beta protein, as in b. (e) Feather keratin, as in b. (f) Chrysopa flava, egg stalk protein, as in b. (Based on Rudall, 21).

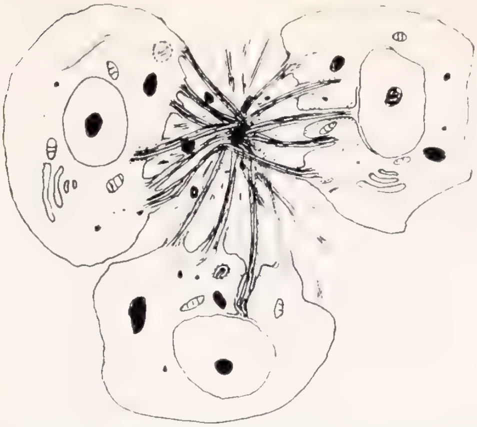

FIG. 3. Outline drawing of three histiocytes in mouse spleen forming amyloid star. Aggregates generally extracellular, in hydrated environment. Poorly preserved outer cell membranes.

ance. Shmueli's x-ray interpretation does not appear to indicate the presence of twisting filaments that are obvious in the electron microscope. In the case of feather keratin, with its similar filaments in the electron microscope, one interpretation (28) of the x-ray diffraction is that beta crystallites 30 Å broad are arranged in a double helical array that gives the appearance of twisting filaments. Another term for this is a macromolecular helix (17), a structure which seems most likely to be present in amyloid on the basis of the accumulated data discussed here.

Amino acid analyses are important but dependent on other data for interpretation. Nyburg for instance states that "There are no really clear-cut classes into which the fibrous proteins can be placed in terms of amino acid composition, but certain differences stand out" (31, p 367). The results of amino acid analysis of Kikkawa et al (9) and Cohen (11), as well as results for wool alpha keratose (oxidized extracted keratin derivative of *low* sulfur content, possibly fibrillar component), gamma keratose (similar *high* sulfur content compound, possibly keratin matrix), and wool root protein are presented in Table II. The keratin analyses are from Mercer (19). In general, inspection of the table shows that there are marked resemblances between amyloid and keratin. Gamma keratose has very high proline and cystine content while alpha keratose contains much glutamic acid. Wool root protein is much like amyloid except for a lower alanine content. It is important to remember that keratins are mixtures of at least two similar proteins, and that the definition of a keratin is not simple.

The traditional view of keratin is "a protein resistant to digestion in pepsin and trypsin, insoluble in dilute acids and alkalis, in water, and in organic solvents." There are also some unacceptable specifications of amino acid content based on very old work (32). Another definition would be an insoluble protein stabilized by disulfide cross-linkages. Mercer (19) reasons that the definition of keratin depends more on process of formation in a cystine-rich

TABLE II

	A	B	C Alpha Keratose	C Gamma Keratose	C Wool Root Protein
Arginine	10.7	7.73	10.35	7.98	8.61
Lysine		6.40	3.84	0.73	5.19
Histidine	5.5	2.23	0.74	0.79	3.74
Tyrosine	3.2	4.68	5.06	2.46	4.35
Tryptophane	2.9	1.71	(range 1.8–2.1, wool)		
Phenylalanine	5.3	5.42	3.67	1.83	3.35
Cystine	3.1	see below	5.11	16.79	3.87
Methionine	1.0	2.51			
Serine	8.0	4.94	8.04	9.83	5.69
Threonine	2.8	3.84	4.69	8.55	4.11
Leucine-(Isoleucine)	4.1	7.81	10.93	3.23	9.48
Valine	3.3	4.91	5.32	4.69	4.47
Glutamic Acid	15.8	11.79	18.33	8.31	13.80
Aspartic Acid	9.3	9.28	9.49	2.30	8.82
Glycine	7.7	5.59	4.42	3.59	4.03
Alanine	13.2	5.77	4.92	2.22	4.42
Proline	4.0	4.62	3.53	10.93	3.17
Hydroxyproline	0	0	0	0	0
Half-cystine		1.64			
Isoleucine			3.73	2.73	3.84

Table in grams amino acid per 100 grams amyloid protein.
A. Kikkawa, Suzuki, Gueft (9); urea-extract spleen.
B. Cohen (11), crude "top layer" liver.
C. Mercer (19).

protein than on any other factor. He also suggests that mixture of a protein with an accessory cystine-rich compound will produce a keratin by cross-linking and stabilizing the structure. One might add certain negative remarks; neither hydroxyproline nor prosthetic groups should be present. Also, very specific x-ray diffractions such as that of collagen should be absent. The amino acid content should not be remarkably high (less than 50 percent) in alanine with glycine, and serine, a combination that leads to the fibroin group of proteins, (or with hydroxyproline, to collagen) which are related to the beta or extended forms of keratin.

Amyloid and Keratin

These proteins show the properties required by the classical definition of keratin. Their amino acid contents are not more different than different keratins are from one another. Their x-ray diffractions have similarities and in special instances are consistent with a very highly organized protein pattern that is not well understood. Electron micrographs of amyloid fibrils, reconstituted previously dissolved feather keratin (24), or of iodinated sonicated wool keratin (30) all show almost identical twisted filaments of similar widths but with different long periods.

The resemblance between these two proteins is further emphasized by the decision at the Groningen Symposium on Amyloidosis (9) to adopt the Mercer (33) terminology for fibrous proteins, which was developed with keratin in mind, but which neatly fits the fibril-filament-protofilament structure of amyloid, since even the structural dimensions correspond rather well. It had been noted that the aggregates, fibrils and filaments of amyloid related closely to corresponding elements of keratin in size and arrangement (23, 24). There was however lacking in the classification scheme a gross fiber, or hair. This was slightly puzzling until it was realized that the huge mass of amyloid is a brittle, firm, transparent, tan material analogous to horn, hoof and fingernail, and scale.

The lack of shape in the amyloid mass is due to its interstitial deposition and nature of fibril formation in intercellular space by nonepithelial (unaligned) cells. In keratin formation, the shape of the horny mass, or fiber, hair, or scale is set by a preexisting well defined group of epithelial cells such as the hair follicle, nail bed, or skin. A similarity of amyloid to keratin is that the thick masses of aggregated fibrils in amyloid may be called tonofilaments, because they are just visible in the light microscope and they look like the intracellular prekeratin tonofilaments seen in squamous epithelium. Thus, aggregates (tonofilaments), fibrils and filaments of similar dimensions exist in both amyloid and keratin. The radiating aggregated fibril masses of both systems (tonofilaments) are present in or near the cytoplasmic borders of both cells. A review of the microscopic appearances of squamous epithelium and early amyloid formation in the spleen of the mouse shows that there is a considerable resemblance between the two cell groups at low electron microscope magnifications (see sketches, Figs. 3, 4). A difference is that the cell borders are vague in amyloid-forming cells, unlike the neat cell borders of cells forming keratin masses. This vagueness of borders in amyloid-forming cells may be explained as a cytorhexis accelerated by the aqueous environment. In keratinization, the cell bodies dry

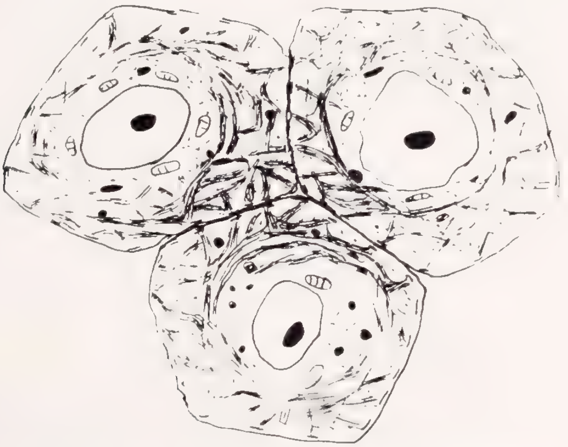

FIG. 4. Outline drawing of three squamous cells forming scaly keratin. Aggregated fibrils intracellular. Outer cell membranes preserved even after cell dies in dry environment.

out and tend to be mummified. Both cellular groups show bands of fine aggregated fibrils. These bands in the squamous cells reach toward those of nearby cells while in amyloidosis, the outer ends of the radiating aggregates tend to meet in a spiny, ball-like mass that was called an "amyloid star" by Jaffé in 1926 (34). The amyloid aggregates are quite regular in number per "star" (about 40), and in fibrils per aggregate (about 16). Now it is possible to note that this arrangement and even the numbers of aggregates and fibrils are roughly in accord with the arrangements of the squamous-cell-producing keratin. Previously, it was thought that the number of coarse amyloid fiber aggregates was related to ergastoplasmic channels (23). Now, one can note the similarity between amyloid and keratin collections and ask if a zone is present in amyloid aggregates corresponding to a desmosome, which is possibly a point of emergence for a tonofilament. I have reviewed many micrographs, but a desmosome-like zone was not seen in amyloidosis. Mercer (19) has suggested that desmosomes appear near areas of cell pores.

The Specific Staining of Amyloid

Keratins are doubly refractile, but they do not take specific amyloid stains such as Congo red and iodine. These staining qualities in amyloid are thought to be associated with its carbohydrate fraction by Ashkenazi, Hersko, Gafni and Heller (35) and by Puchtler, Sweat and Kuhns (36). Removal of the polysaccharide seems to cause loss of Congo red staining. At one time it was suggested that the amyloid protein fibril was constructed in some way like cellulose, and these special stains were trapped nonionically within a tubular fibril as has been demonstrated for cellulose and dextrins by Cramer (37), and others. This surmise is made likely by the presence of 20 percent polysaccharide content in amyloid since most molecules that take these special stains are fibrous polysaccharides that will allow the formation of inclusion compounds, namely, chitin, cellulose, and dextrin. Other compounds such as polyvinyl alcohol and polyvinylpyrrolidone that take these stains have similar molecular arrangements. The well known Congo red green-birefringence in amyloid is probably due to the influence of the surrounding amyloid molecule on the molecular alignment of the Congo red included in the amyloid, just as methylene blue changes color when it is dissolved in cyclodextrin solution. Iodine staining amyloid in a like manner probably forms the long straight "metallic" polyiodide molecule as found in cellulose (37).

One may ask if amyloid acquires its polysaccharide component at the moment of extrusion, since the fibril is formed at a cell edge and extends into the intercellular space. Analogous but reversed events are known to take place in insects as in the formation of insect cocoons, when the silk fiber becomes coated by another protein, or, a chitinous fiber becomes coated by protein (21).

Keratin might be expected not to acquire a polysaccharide addition from the plasma during fiber formation which remains intracellular. In addition, it is known with keratin that matrix proteins and cell fragments contribute to the keratin mass, further shielding it from ground substance as the mass forms, dries, and moves centrifugally from the body. The well-known denseness of keratins, as well as their fibril-plus-matrix arrangement, may forbid the inclusion mechanism of staining, which requires an intramolecular space.

In addition to the question of specific staining, it is appropriate to mention that amyloid is not as strong as keratins generally, since it is somewhat brittle. In terms of polymer chemistry this may be due to the prevalence of short lengths of fibrils without good alignment as seen with electron microscopy (38).

It is possible that the very specific amyloid stain has in the past interfered to some extent with the recognition of important common properties of amyloid and keratin.

Amyloidosis can be described as a dysplasia of mesothelial cells in which they produce a protein remarkably like the keratins but associated with polysaccharide that causes a unique staining reaction. Amyloidosis may be termed therefore a special form of keratosis or keratotic dysplasia.

The property of forming keratin is a common attribute of epithelial cells of any type. Keratinizing dysplasias and metaplasias have been widely reported in epithelia since the early days of descriptive pathology, and if one keeps in mind the wide distribution of keratin in living things (even in low metazoa, 19) it is not completely unexpected that cells of mesenchymal origin may under some unknown stimulus form a keratin very much like those of the epithelial cells, but in a different or hydrated internal environment filled with ground substance proteins and complex carbohydrates. This hypothesis brings together the epithelium-associated amyloids (calcifying epithelioma of skin (39), calcifying odontogenic tumor (40), beta cell tumor (41), diabetic pancreas island (42), carcinoma of the thyroid and lung (43), and the mesenchymal amyloids. It is worth noting that corpora amylacea of the prostate take amyloid stains, have fibrillar ultrastructure, and yield amino acid analyses like those of keratin. Schrodt and Murray have suggested that these corpora are keratin (44). Micro-x-ray diffractions of corpora amylacea have shown unoriented rings in my experience.

Implicit in the above hypothesis are suggestions that amyloid and keratin fibrils share precursor substances and pathways, and that the matrix components are probably quite different in two proteins.

Missmahl (45) recently has favorable results on treating amyloidotic patients with methotrexate. Although this powerful antifolic acid compound affects many different cells, it is interesting to associate this result with the success of methotrexate therapy in psoriasis, which is an inborn dysplasia of skin cells with disturbances of keratinization. Also, some cases associating psoriasis with amyloidosis have been reported (47).

Conclusion and Summary

A review of electron microscopic, x-ray diffraction, and amino acid analyses of secondary amyloid compared with similar analyses of keratins indicate that the two fibrous proteins have many resemblances. Amyloid may be considered a member of the group of keratin proteins, especially the beta keratins, a member secreted mostly by histiocytes and mesenchymal cells, but also by epithelial cells, with an additional component of polysaccharide. Amyloid structure appears to be best described as a macromolecular helix. The specific staining qualities of amyloid differ from those of keratin, possibly as a result of different alignment of fiber or polysaccharide content. Amyloidosis thus may be considered a dysplasia of mesenchymal or epithelial cells, resulting in the extracellular deposition of a pathological keratin-like scleroprotein.

Acknowledgment

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On Pedunculated Adenomatous Polyps of Colon and Rectum with Particular Reference to Their Malignant Potential

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The dictum that a considerable proportion of adenomatous polyps of the colon and rectum undergo a malignant change has been challenged in recent years by several investigators. Spratt, Ackerman, and Moyer (1) failed to find any unequivocal carcinoma among 425 adenomatous polyps, nor did they find any residual adenomatous area among 325 carcinomas. Furthermore, they found a difference in distribution patterns between carcinomas and adenomatous polyps and no difference in the age occurrence of the two lesions. Spratt and Ackerman (2) in a separate study reported that they found no evidence of preexisting adenomatous polyps in 20 small colonic carcinomas under 2 cm in diameter. On the basis of these findings, they raised certain doubts as to the malignant potential of adenomatous polyps.

More recent work by Castleman and Krickstein (3) on the same material which had previously been studied by Welch et al (4) again denied the malignant potential of adenomatous polyps. The latter had originally reported that they found six carcinomas arising in 27 villous adenomas and 54 carcinomas in 295 adenomatous polyps, either pedunculated or sessile. Castleman and Krickstein reviewed 59 of those 60 carcinomas and reclassified them as follows: one adenomatous polyp with carcinoma; 33 adenomatous polyps without carcinoma; five villous adenomas with carcinoma; four villous adenomas without malignant change; 14 polypoid carcinomas. They attributed the originally reported high incidence of carcinomatous change in adenomatous polyps to errors in interpretation of the lesions and emphasized the importance of applying strict criteria for malignant change and of distinguishing adenomatous polyps from villous adenomas and polypoid carcinomas.

Recognizing the importance of an understanding of the true nature of adenomatous polyps, particularly of their malignant potential which determines the therapy of these lesions, we have undertaken, at the urging of Dr. Otani, to restudy the material seen at this institution, with special attention to the behavior of pedunculated adenomatous polyps which had been considered less dangerous by many.

Material and Methods

Four hundred and fifty-eight pedunculated lesions of the colon and rectum which had been classified originally as adenomatous polyps with or without carcinomatous change were collected from the file of Surgical Pathology Laboratory of The Mount Sinai Hospital. They had been accessed between 1948 and

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1962. Most of them were removed by simple polypectomy, some by short segmental resection, and still others found incidentally in the colectomy specimens of noncancerous nature. Villous adenomas and cases of multiple or familial polyposis were not included because their malignant potential was not at issue. In all 458 polyps the entire tip and pedicle were available for histological examination.

A typical adenomatous polyp is characterized by proliferating glands which are short and separated by a relatively wide stroma. Aggregates of neoplastic glands tend to form globular forms around the fibrous core. Nuclear and cellular polarity is well maintained. A pedicle consists of stretched nonneoplastic mucosa and submucosa linking adenomatous proliferation and normal mucosa (Fig. 1). A villous adenoma as illustrated in Figure 2 shows numerous long villi projecting directly from the fibrous core and an extremely slender stroma supporting the proliferating epithelium. Nuclear and cellular polarity is well maintained. Although these 458 polyps were all originally classified as adenomatous polyps, as we reviewed them it soon became evident that many, especially larger ones, contained villous component. An adenomatous polyp containing villous component is shown in Figure 3. In order to find a relation between size of the polyps and occurrence of villous component, in 100 consecutive polyps their greatest diameter was measured and correlated with the presence of villous component.

Carcinomatous changes are characterized by irregularity of size and shape of proliferating glands or epithelia, loss of nuclear and cellular polarity, increase

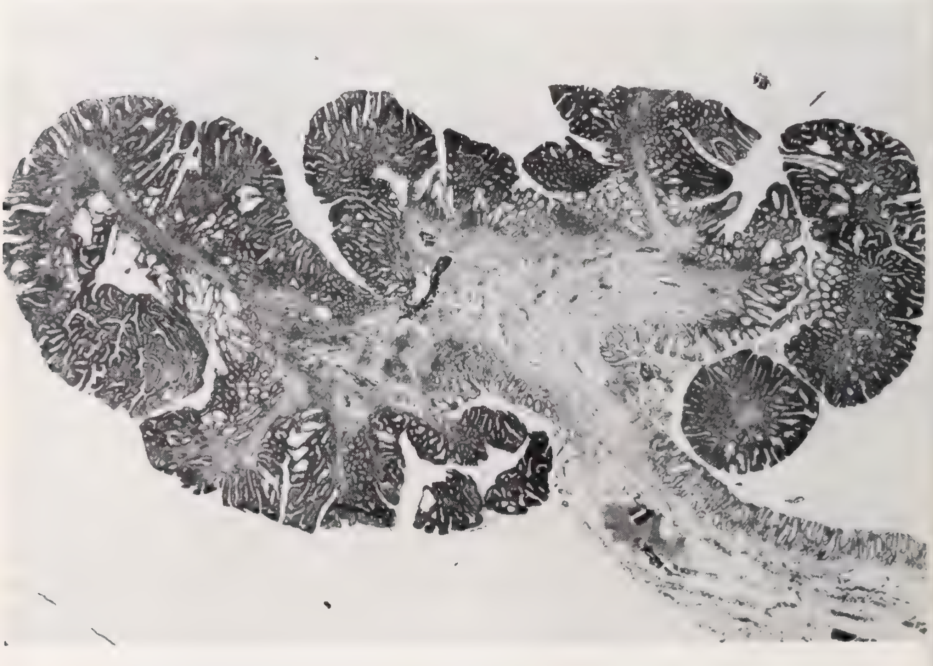

FIG. 1. Typical pedunculated adenomatous polyp. Magnification × 7, H&E.

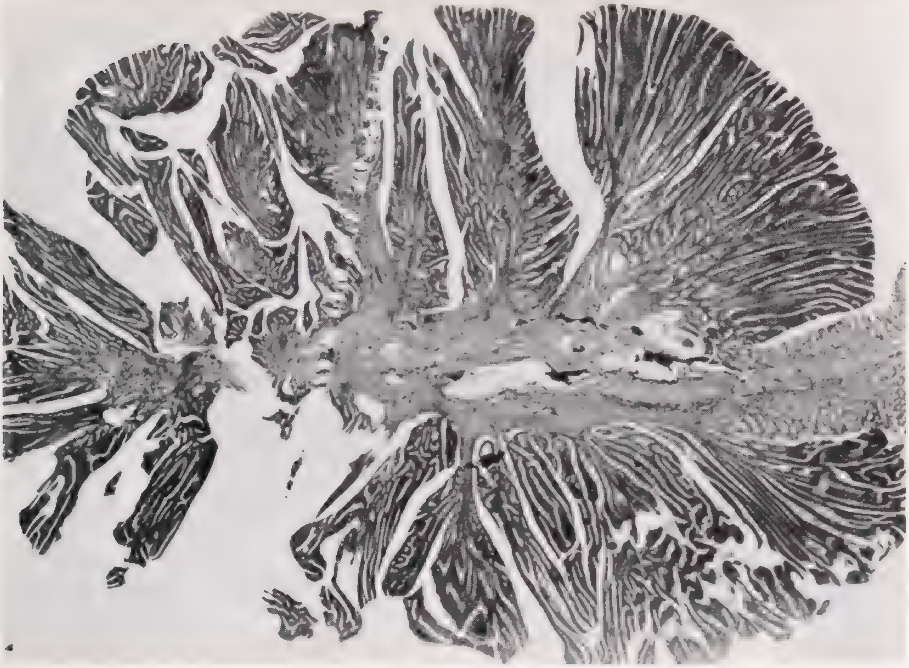

FIG. 2. Typical pedunculated villous adenoma. Magnification × 7, H&E.

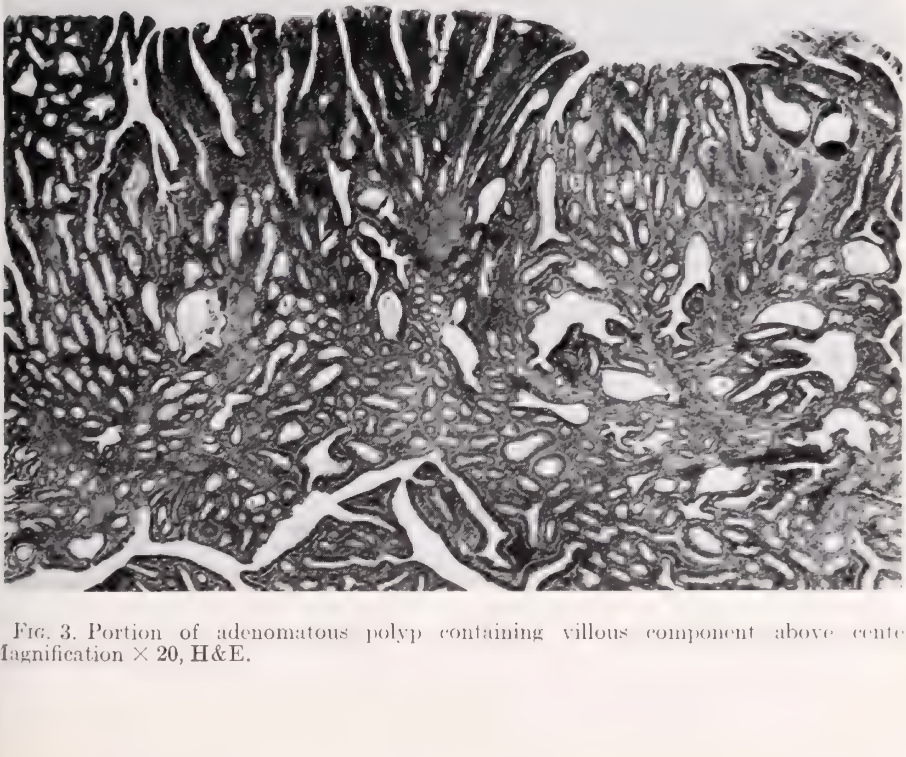

FIG. 3. Portion of adenomatous polyp containing villous component above center. Magnification × 20, H&E.

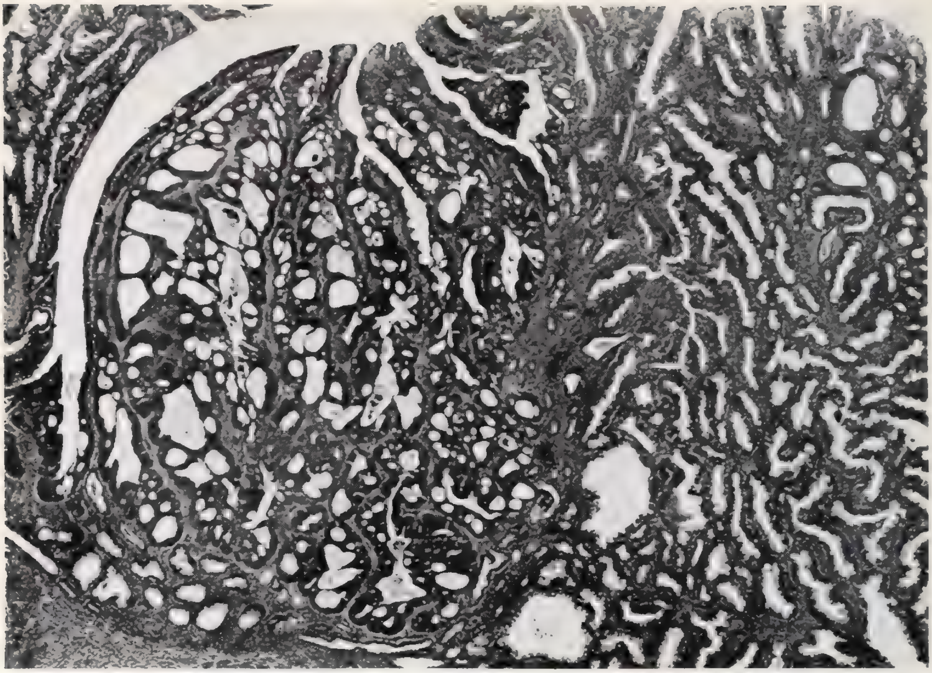

FIG. 4. Adenomatous polyp with focus of noninfiltrating adenocarcinoma in center left. Magnification × 20, H&E.

FIG. 5. Adenomatous polyp containing focus of infiltrating adenocarcinoma. Magnification × 20, H&E.

of cytoplasmic basophilia, and desmoplastic reaction when infiltration takes place (Figs. 4 and 5). In all the cases showing a carcinomatous change the size of the polyps was measured and again correlated with the occurrence of villous component. The invasion of the stroma and pedicle and metastatic deposit in the regional lymph nodes when available were checked. In addition, sex and age of the patients, location of the polyps, treatment, and clinical courses were recorded.

Results

As shown in Table I, the majority of the polyps 10 mm or smaller in diameter were of a pure adenomatous type. On the other hand, the polyps over 10 mm in diameter showed an increasing tendency to contain villous component with increasing size of the polyps. We found 43 polyps with carcinomatous change—an incidence of 9.4 percent. Of these 14 were in pure adenomatous polyps and 29 in polyps with villous component. Since about 69 percent of the polyps in this series were of a pure adenomatous type, the incidence of malignant change in pure adenomatous polyps was calculated to be about 4 percent, whereas the incidence of malignant change in polyps with villous component about 20 percent. However, histologic evidence showing carcinomas arising directly from villous areas was inconclusive in our material. Table II illustrates relation between the size of malignant polyps and the presence of villous component. There was no malignant change in the polyps under 5 mm in diameter, whereas the polyps over 10 mm in diameter showed a higher incidence of carcinomatous change. As for the extent of carcinomatous change, five cases exhibited small

TABLE I

Correlation between Size of Polyps and Occurrence of Villous Component in 100 Consecutive Polyps

Diameter of Polyps	≤5 mm	6–10 mm	11–15 mm	16–20mm	21–25 mm	≥26 mm	Total
No. Pure Adenomatous Polyps	3	32	22	8	4	0	69
No. With Villous Component	0	3	10	10	4	4	31
Total	3	35	32	18	8	4	100
% With Villous Component	0	8	31	55	50	100	31

TABLE II

Correlation between Size of Polyps and Occurrence of Villous Component in 43 Cases with Carcinomatous Change

Diameter of Polyps	≤5 mm	6–10 mm	11–15 mm	16–20mm	21–25 mm	≥26 mm	Total
No. Pure Adenomatous Polyps	0	6	4	4	0	0	14
No. With Villous Component	0	2	9	13	3	2	29
Total	0	8	13	17	3	2	43
% With Villous Component	0	25	69	76	100	100	67

single or multiple foci of noninfiltrating carcinoma (Fig. 4). The remainder showed infiltrating carcinomas to varying degree (Fig. 5). In addition, the pedicle was invaded in four cases, one of which also showed tumor invasion of the submucosal lymphatics and veins of the pedicle (Figs. 6, 7, and 8). Two cases treated by segmental resection showed stromal infiltration as well as nodal involvement. There were 25 men and 18 women. 30 cases were treated by simple polypectomy and 13 cases by segmental resection. As far as distribution of the polyps is concerned, three were in the transverse colon, three in the descending colon, 35 in the sigmoid colon, and two in the rectum. These figures, however, may not represent a true distribution pattern because polypectomy is usually performed more frequently on the left side of the colon. Age occurrence of 100 consecutive benign polyps and 43 malignant polyps is correlated in Table III. Ten percent of benign polyps belonged to the patients under 40 years of age and no malignant polyp was found in this age group. The age occurrence patterns over 40 years of age showed almost parallel relation between benign and malignant polyps. Follow-up study was by no means complete, but as far as we could gather, the following results were obtained: Three patients have died of unrelated causes. Two patients, a 60-year-old woman and an 83-year-old man, had an adenomatous sigmoid polyp with a focal carcinoma infiltrating the stroma removed by polypectomy. Both patients died of generalized carcinomatosis five and seven years later, respectively. In both cases, no other primary was clinically known, but no autopsy was performed. Two patients, a

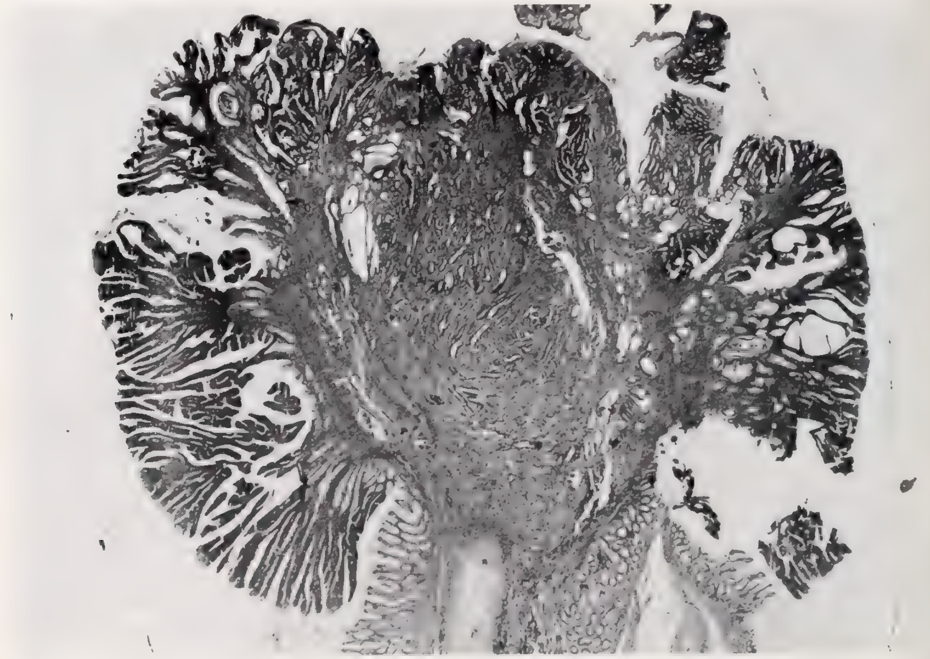

Fig. 6. Polyp of mixed type showing infiltrating adenocarcinoma which invaded stroma and upper pedicle. Magnification × 7, H&E.

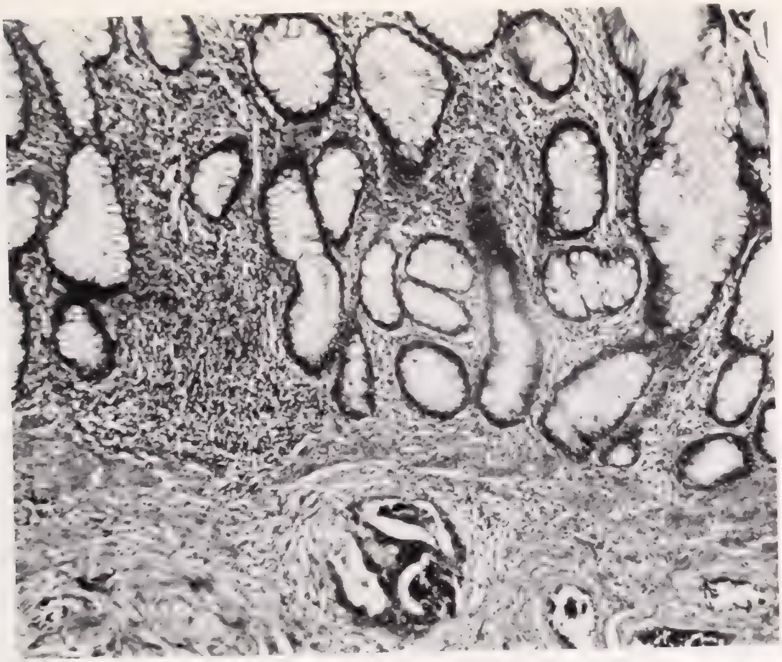

FIG. 7. Same polyp as in Fig. VI showing invasion of submucosal lymphatic of pedicle by carcinoma. Magnification × 100. H&E.

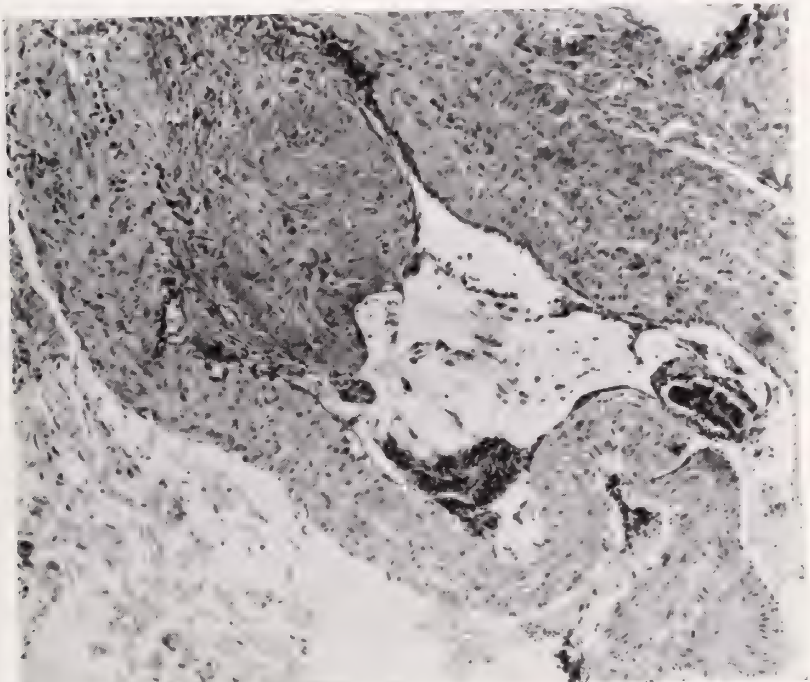

FIG. 8. Same case as in Fig. VI and VII showing tumor thrombus in submucosal vein of pedicle. Magnification × 100, H&E.

TABLE III

Age Occurrence of Polyps with and without Malignant Change (%)

	Age						
	≤30	31–40	41–50	51–60	61–70	71–80	≥81
Benign... ...	3	7	17	34	29	10	0
Malignant................	0	0	18	40	28	12	2

63-year-old woman and a 71-year-old man, had a similar lesion in the sigmoid and descending colon, respectively which had been treated by simple polypectomy and they developed a large infiltrating carcinoma in the same segment of the colon four and a half and seven years later, respectively. A 54-year-old woman had a malignant polyp of the sigmoid colon which is shown in Figs. 6, 7, and 8 and was treated by polypectomy but came back with a large infiltrating carcinoma of the same segment of the colon six years later. Interestingly, two other patients, 49- and 66-year-old men, treated by segmental resection for the metastasizing malignant polyps in the descending and sigmoid colon, respectively are well eleven and six years later. Histologic examination of the carcinomas which developed later in these patients yielded no clear evidence to ascertain if they were an independent primary or recurrence.

Discussion

Probably many carcinomas of the colon and rectum arise directly from the normal mucosa; and their development is frequent in conditions such as chronic ulcerative colitis, multiple or familial polyposis, and villous adenoma. However, it becomes apparent from this study that a significant proportion of pedunculated polyps, either pure adenomatous polyps or polyps containing villous component, also may undergo carcinomatous change. Although a higher incidence of carcinomatous change (20 percent) was found among polyps with villous component than among pure adenomatous polyps (4 percent), histologic evidence showing a carcinoma arising exclusively from a villous area was inconclusive in our material.

An adenomatous polyp has been considered a neoplastic growth of mucosal glands while villous adenoma a neoplastic proliferation of mucosal surface epithelium (5).

In about one-third of the polyps studied, both adenomatous and villous features coexisted and this tendency became greater with increasing size of the polyps. The high incidence of coexistence suggests that the two patterns may reflect a single neoplastic process of mucosal epithelium which may have variable patterns of expression. Since we have studied only surgically resected polyps, and polypectomy is more frequently performed for left-sided lesions of the colon, the distribution patterns of both benign and malignant polyps in this series do not represent a true picture.

Approximately 10 percent of benign polyps were found in the age group under 40, whereas no malignant polyp was found in this age group. Thus there seemed to be a ten-year gap between the occurrence of benign and malignant polyps. Our finding in this respect differs from the findings of Spratt, Ackerman, and Moyer (1).

Evolution of invasive carcinomas in certain circumstances, such as uterine cervical carcinomas, is an extremely slow process. Thus the difference we observed in the age occurrence of benign and malignant polyps is of some interest in this light. Although we cannot be absolutely certain whether the infiltrating carcinomas developing in three patients were recurrences or separate primary tumors, it would seem unlikely on a statistical basis that in all three cases independent carcinomas developed in the same segment of colon from which previous adenomatous polyps had been resected.

Our follow-up study was by no means complete, but as far as we could gather many patients have done well with simple polypectomy. However, from the experience of our two fatal cases, the three cases in which carcinoma developed later and the two cases that were successfully managed by segmental resection despite nodal involvement, it would appear that in those cases with polyps showing more extensive carcinomatous change or invasion of the pedicle segmental resection including dissection of the regional lymph nodes would be the preferred method of treatment.

Summary

458 surgically resected pedunculated polyps of the colon and rectum were studied. About one-third of the polyps were found to contain villous component. There was an increasing tendency for the presence of villous component with increasing size of the polyps. It was assumed that adenomatous and villous features are different expressions of the same neoplastic process involving mucous membrane of the colon and rectum.

Forty-three among 458 polyps showed carcinomatous change—an incidence of 9.4 percent. Of 43 malignant polyps, five were noninfiltrating and the remainder infiltrating. The incidence of carcinomatous change was greater in polyps containing villous component (20 percent) than in pure adenomatous polyps (4 percent).

Judging from the results of follow-up study, polyps with small foci of carcinomatous change will do well by simple polypectomy; on the other hand, polyps with more extensive carcinomatous change or invasion of the pedicle should be treated by segmental resection including removal of regional lymph nodes.

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Eosinophilic Membranes of Mammary Terminal Ducts and Acini: Diagnostic Significance of Their Absence in Infiltrating Malignant Lesions

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Normal breast terminal ducts and acini have an intact, encircling, closely adherent eosinophilic membrane (EM) in hematoxylin and eosin stained sections observed by light microscopy. The absence of the EM has been used by us as a helpful diagnostic aid in filtration in malignant epithelial breast lesions, especially during frozen section consultation and in well-differentiated, histologically innocent-appearing adenocarcinomas. A search of the literature reveals only one reference to this observation (1) and has stimulated us to review a series of malignant epithelial breast lesions to determine the validity of this observation.

Material and Methods

Sixty-seven malignant epithelial tumors of the breast biopsied and/or radically resected at Sinai Hospital during 1969 were reviewed for the presence or absence of eosinophilic membranes in the areas of infiltration. Adjacent normal breast tissue or breast tissue with benign pathologic alterations served as controls for the observation of the presence of the EM. All tissue had been fixed in 15% formalin, paraffin sectioned, and hematoxylin and eosin stained. Frozen section preparations, which had been stained with hematoxylin and eosin, dehydrated and coverslipped with permount were available for review. A gradual lowering of the substage condenser of the microscope was found to increase the definition of the EM in hematoxylin and eosin stained sections. Special stains including periodic-acid Schiff, reticulum, and Masson trichrome were used but not found to be particularly helpful. The malignant lesions were classified according to the Atlas of Tumor Pathology of the Armed Forces Institute of Pathology (2).

Results

The histologic types of malignant epithelial breast lesions reviewed are listed in Table I.

The normal eosinophilic membrane observed by light microscopy is a dense, homogeneous structure measuring approximately 10,000 A in thickness and is closely adherent to the basilar epithelial cells and myoepithelial cells of the terminal ducts and acini (Fig. 1). An EM was present in all benign terminal duct areas of the breast tissue controls. The EM was hypertrophic in various benign pathologic alterations such as chronic inflammation (Fig. 2) and sclerosing adenosis. The EM was also hypertrophic in residual normal ducts in an area

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infiltrated by carcinoma (Fig. 3). Occasionally the EM became confluent with the adjacent hyalinized connective tissue stroma in sclerosing papillomatosis.

Fifty-nine malignant epithelial breast lesions showed complete absence of an EM in the areas of tumor infiltration of the breast connective tissue stroma (Figs. 4–6). The majority of these infiltrating lesions involved a direct extension into the stroma and were not extensions within intramammary lymphatics. An intact EM was present in noninfiltrating foci of either intraductal or lobular carcinoma-in-situ observed in some of the infiltrating malignant lesions. Beginning infiltration of a predominantly in-situ carcinoma could be determined easily by the absence of an EM in one focus where tumor cells were spreading to the breast connective tissue stroma.

Seven of the malignant epithelial breast lesions had a partial EM in the areas of tumor infiltration (Fig. 7). The partial EM was easily distinguishable from the intact EM of the benign breast tissue. The partial EM appeared to be composed of focally condensed connective tissue stroma in an area of infiltration. Those infiltrating carcinomas composed of myoepithelial cells in addition to epithelial cells had a higher proportion of the partial EM.

The following is a histologic classification of 67 malignant epithelial breast lesions reviewed for the year 1969:

TABLE I

Infiltrating duct carcinoma with productive fibrosis	50
Infiltrating duct carcinoma and Paget's disease	1
Infiltrating duct carcinoma and lobular carcinoma-in-situ	2
Infiltrating duct carcinoma and infiltrating lobular carcinoma	1
Infiltrating duct carcinoma and colloid carcinoma	2
Infiltrating duct carcinoma, colloid carcinoma, and tubular carcinoma	1
Colloid carcinoma	2
Tubular carcinoma	1
Medullary carcinoma	1
Infiltrating comedocarcinoma	2
Infiltrating comedocarcinoma and Paget's disease	1
Infiltrating papillary carcinoma	1
Infiltrating lobular carcinoma	1
Lobular carcinoma-in-situ in a fibroadenoma	1
	67

Discussion

The eosinophilic membrane surrounding the terminal ducts and acini in normal breast tissue, breast tissue with benign pathologic alterations, and breast tissue with non-infiltrating, malignant lesions is not analogous to the basement membrane observed by electron microscopy. The EM observed by light microscopy is approximately ten times thicker (10,000 A) than the basement membrane which measures approximately 1000 A (3 4). The EM is composed of the basement membrane and adjacent collagen fibers which together form the discrete membrane. The electron microscopic observation of a basement membrane

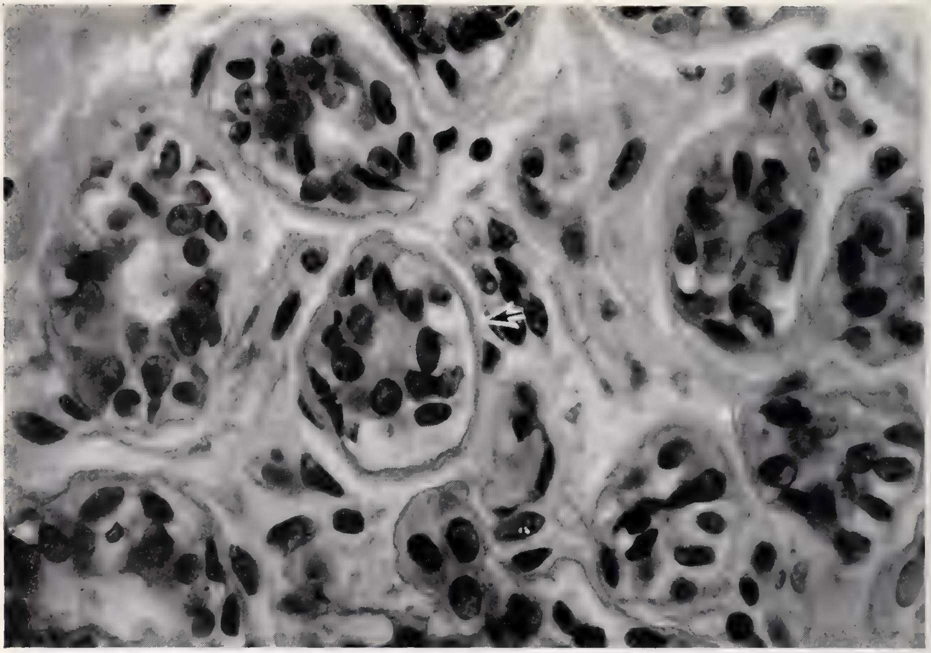

FIG. 1. Eosinophilic membrane (arrow) closely adherent to the terminal ducts of normal breast tissue (hematoxylin and eosin × 880).

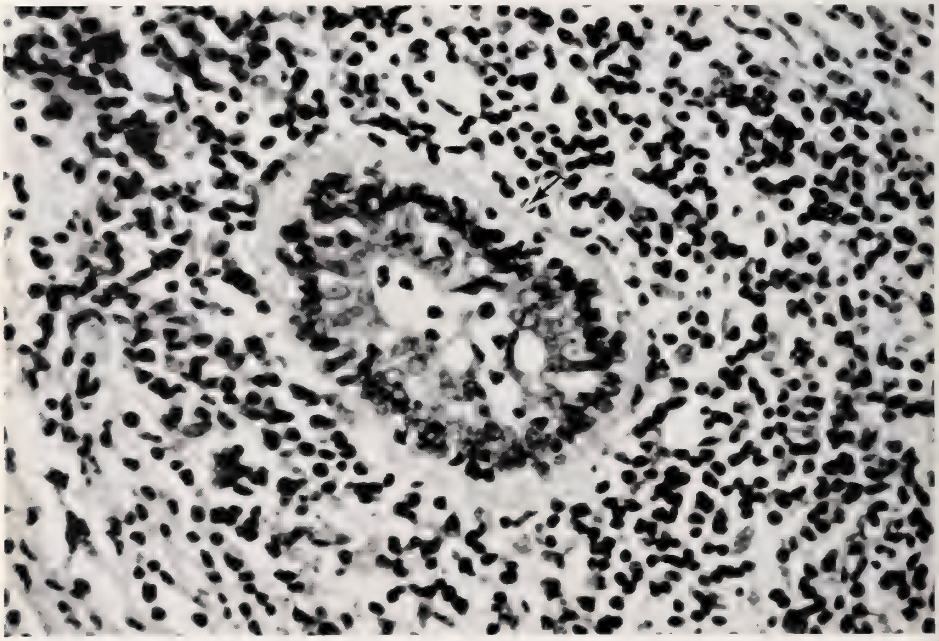

FIG. 2. Hypertrophic eosinophilic membrane (arrow) of terminal duct with epithelial proliferation in an area of chronic nonspecific mastitis (hematoxylin and eosin × 325).

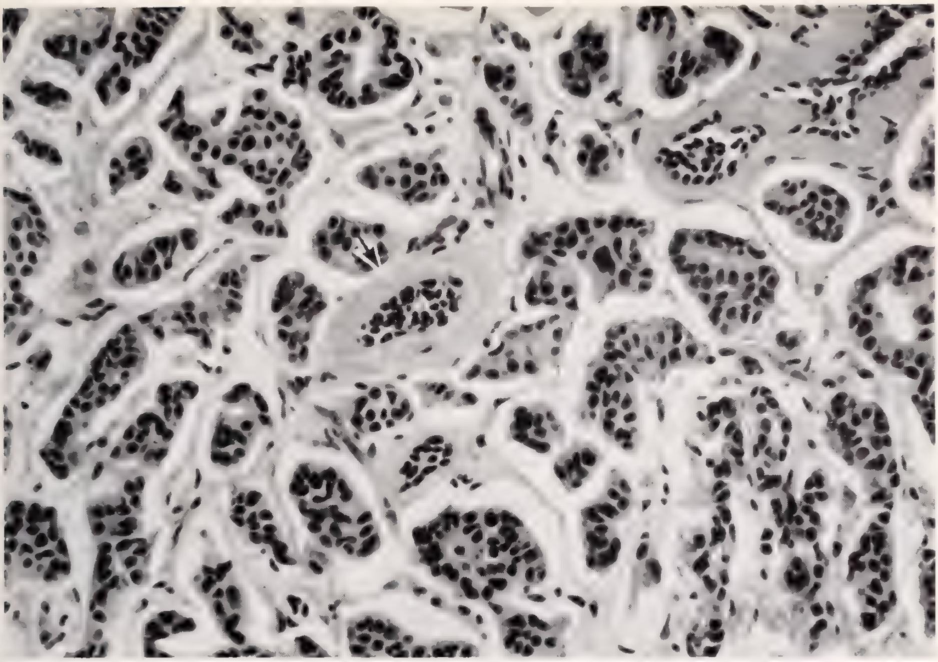

FIG. 3. Hypertrophic eosinophilic membrane (arrow) around residual breast terminal duct in an area infiltrated by an adenocarcinoma (hematoxylin and eosin × 352).

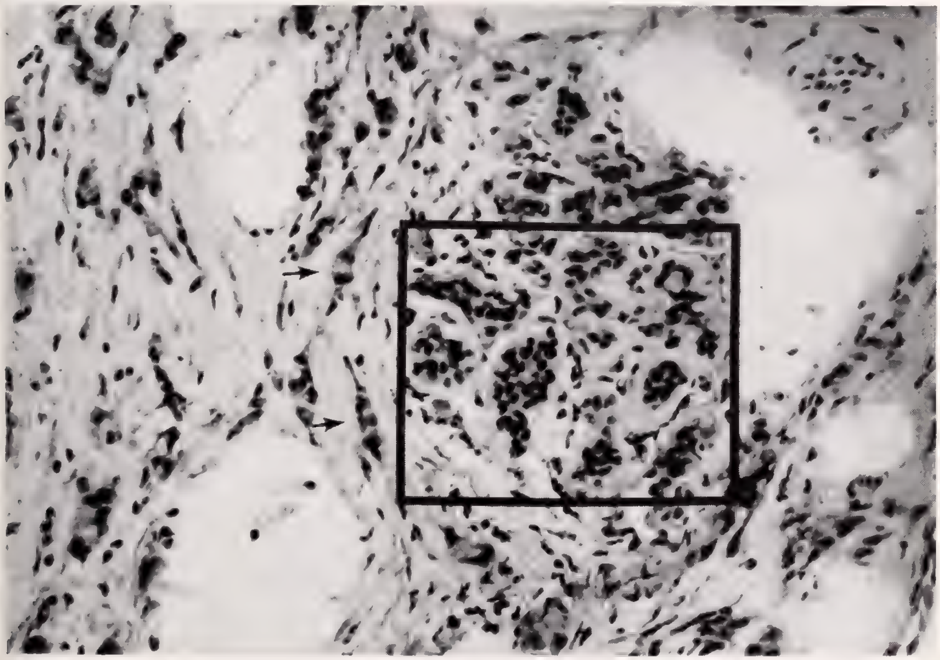

FIG. 4. Cryostat frozen section of breast tissue showing infiltrating carcinoma cells (arrows) without eosinophilic membranes, adjacent to terminal ducts with thickened eosinophilic membranes (rectangle) (hematoxylin and eosin × 352).

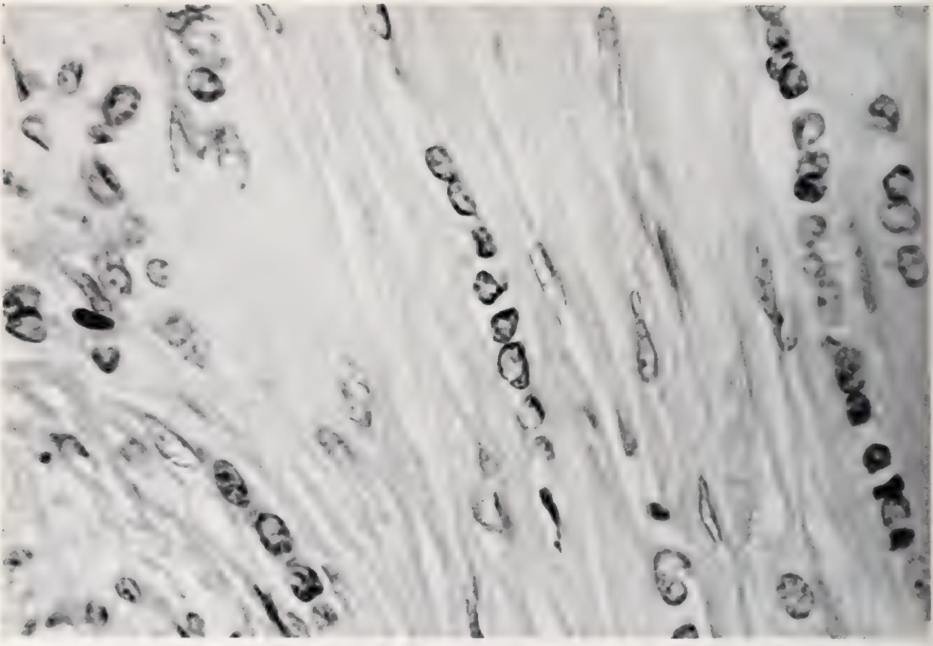

FIG 5. Scirrhous carcinoma (infiltrating duct cell carcinoma with productive fibrosis) of breast with absence of eosinophilic membranes around infiltrating cells (hematoxylin and eosin × 880).

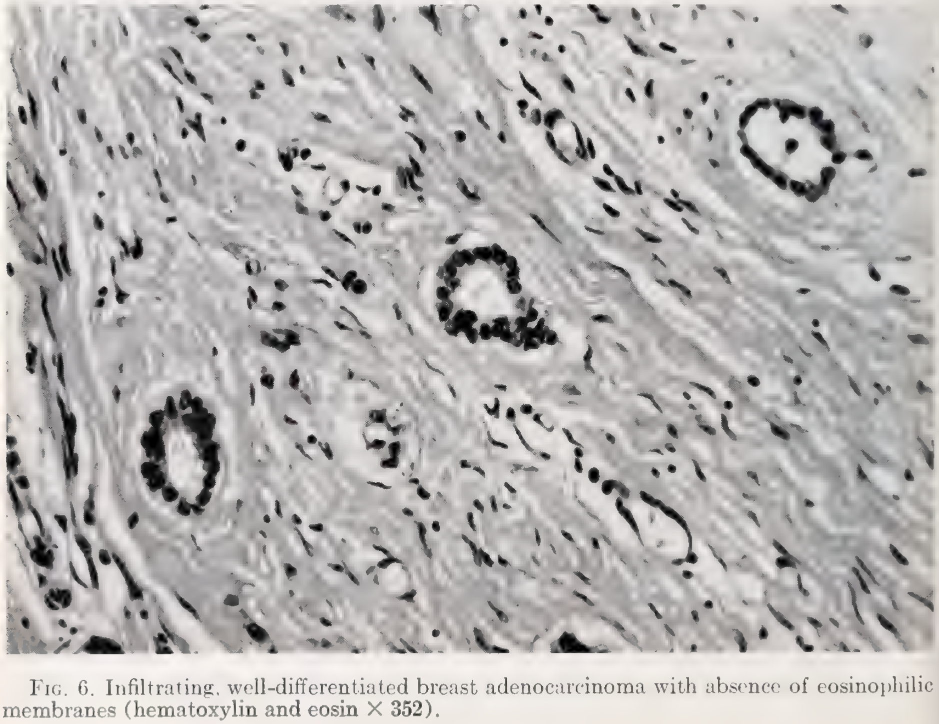

FIG. 6. Infiltrating, well-differentiated breast adenocarcinoma with absence of eosinophilic membranes (hematoxylin and eosin × 352).

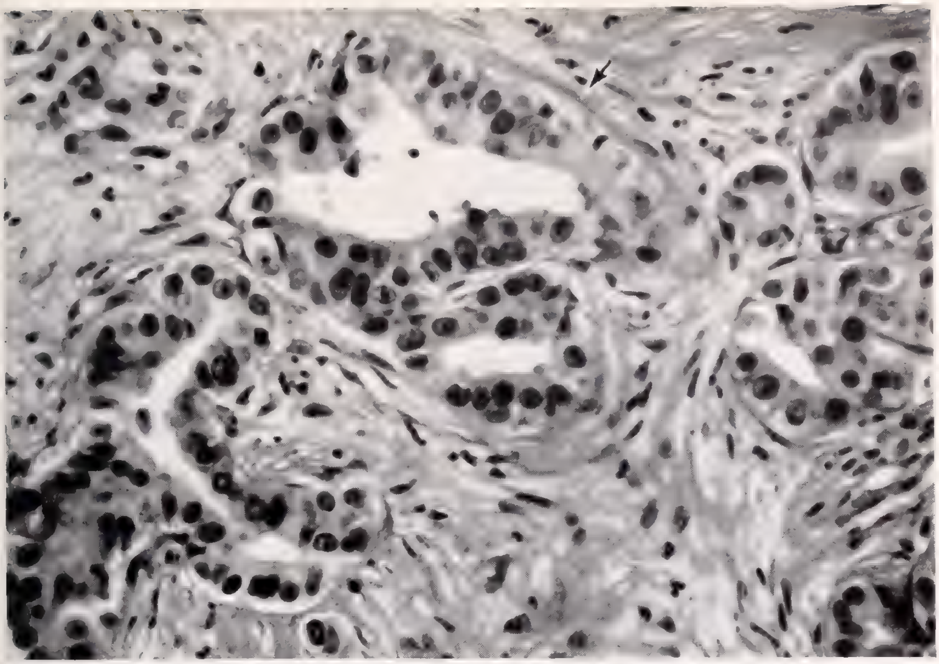

FIG. 7. Infiltrating breast adenocarcinoma with a partial eosinophilic membrane (arrow) (hematoxylin and eosin × 560).

in scirrhous carcinoma, as opposed to its absence in medullary carcinoma, as a means of differentiating these two carcinomas (5) would not be relevant to this discussion since this basement membrane is not observed by light microscopy.

A perusal of the literature has failed to reveal any mention of the significance of the eosinophilic membrane in histopathologic diagnosis of infiltrating breast lesions either in the older literature such as Ewing's textbook where a residual breast duct with a hypertrophic EM is depicted surrounded by carcinoma cells devoid of an EM (6), or in a most recent article describing infiltrating, well-differentiated, innocent-appearing adenocarcinomas (7). The only reference to the absence of an EM in infiltrating malignant breast lesions is an incidental observation in a study of lobular carcinoma (1).

The low-power histopathologic pattern is the most important diagnostic observation in determining the presence or absence of infiltration in malignant epithelial breast lesions. In certain instances, however, the diagnosis of infiltration is not easily determined, such as, 1) during frozen section consultation where the thickness of the section and limited sampling are factors and 2) in well-differentiated, innocent-appearing adenocarcinomas. The results of this study support the observation that partial or complete absence of an EM in malignant breast epithelial lesions is diagnostic of infiltration.

Summary

Normal breast terminal ducts and acini have an intact, encircling, closely adherent, eosinophilic membrane observable by light microscopy. The observation of total absence (59 cases) and partial absence (7 cases) of this eosinophilic membrane in the malignant mammary epithelial lesions studied is considered diagnostic of infiltration, in addition to the low-power microscopic histopathologic pattern.

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Editorial Colophon

This tribute to Dr. Sadao Otani is admittedly amorphous. What unifying theme there is has several purposes: 1) to present in words a picture of this loved man, so vividly done by Dr. Hans Popper and Dr. Joseph Ehrlich; 2) to describe the methods of the man at his work and in his teaching detailed by Dr. Ken Mori; 3) to preserve some posthumous and hitherto unpublished gleanings from his notes, a laborious task undertaken by Dr. Milton Kannerstein and Dr. Irving Ratner; and 4) to present, from each cohort of his pupils from senior to most junior, five original articles in the traditional Festschrift form. Scores more would have been forthcoming had space been available.

The Editor acknowledges in deep gratitude the tireless work of the Guest Editors Dr. Lotte Strauss and Dr. Jacob Churg, without whose efforts this issue would not have come to fruition.

LESTER R. TUCHMAN, M.D.

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Arnold M. Katz, M.D.
And Guest Lecturers.

April 21, 1972
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ALICE IDA BERNHEIM, M.D.
1905–1971

In Memoriam

ALICE IDA BERNHEIM, M.D.
1905–1971

With her untimely death on September 12, 1971, Mount Sinai mourns the loss of one of the most capable and dedicated members of its staff. Alice Bernheim was born on December 27, 1905 in New York City. She attended Horace Mann High School, and received her college education at Wellesley College and her M.D. degree from the College of Physicians and Surgeons, Columbia University in 1931. Her association with The Mount Sinai Hospital, which was to last throughout her professional life, began with her internship that same year. In 1932 she was appointed Research Assistant in Morbid Anatomy, a position she held until 1942. Concurrently, from 1934 to 1938, she also held an appointment as Clinical Assistant in the Outpatient Department (Gynecology and Medicine). From 1942 until 1955 she held positions as Assistant Pathologist and later as Associate Pathologist, and from 1955 as Research Associate in Pathology under the direction of Dr. Hans Popper. She was a Diplomate of the American Board of Pathology.

Dr. Bernheim combined outstanding ability with a deep sense of commitment. Dr. Paul Klemperer, Director of the Pathology Department when she first came to Mount Sinai, recognized her competence as well as her rare personal qualities. Their close professional association spanned more than 20 years. In fact, together with Dr. Sadao Otani, she became one of Dr. Klemperer's most valued associates. Alice placed herself totally at the service of the hospital, taking on an ever-increasing share of the administrative chores in the Department of Pathology, in addition to her responsibilities for the autopsy service, and for surgical pathology (which she shared with Dr. Sadao Otani). The demands on her were considerable, especially during the difficult years of World War II, when the pathology department was short of experienced staff. Living within walking distance of the hospital, she made herself available at all hours, never sparing herself, and invariably giving her best without regard for personal or material rewards. At all times she was motivated by an overriding concern for the welfare of the patients. Beneath her gentleness and modesty was hidden an almost superhuman strength founded on unfaltering self-discipline.

While Dr. Bernheim regarded service as her primary mission as a physician, she nonetheless found it possible to engage in scientific research which resulted in publications of outstanding merit. Her research was initially concerned with the generalized Shwartzman phenomenon, in which she collaborated with Dr. Gregory Shwartzman and with Dr. Isadore Gerber. In one of the earliest case reports of thrombotic thrombocytopenic purpura (Moschcowitz' Disease) published in 1943, she called attention to the need for studies of the blood clotting mechanism in this disease. Much of her investigation was carried out in collaboration with her husband, Dr. Abraham Penner. The work originated in observations, made at the autopsy table, of visceral lesions in patients who had suffered shock. These careful studies reported in a concise and lucid style (in 1939 and 1940) suggested that the lesions were initiated by local circulatory changes under systemic control, i.e., that they represented a part of the homeostatic mechanisms called into play in shock. In a series of ingeniously conceived animal experiments, components of these mechanisms were investigated with particular reference to their gastrointestinal and renal manifestations. These investigations which were initiated prior to 1940 and resumed after World War II, have contributed to a vastly improved understanding of the genesis of various types of ulcerative lesions of the digestive tract, as well as of renal cortical necrosis.

Notwithstanding her earnest involvement with her profession and its exacting demands on her energies, Alice was a deeply devoted wife, a no less devoted mother of two sons, David and Daniel Penner, and a concerned and loyal friend. The love that reigned in her home was the fountain spring of her life. She enjoyed the love and respect of all those who were fortunate to know her, for she was a truly beautiful human being.

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A New Concept in Circulatory Assistance—The Dual-Chambered Intraaortic Balloon*

DAVID BREGMAN, M.D. AND ROBERT H. GOETZ, M.D.

It has been estimated by the President's Commission on Heart Disease, Cancer, and Stroke that 3.1 million Americans have definite coronary artery disease and that over 500,000 persons die of this disease each year in the United States. The crude death rate from coronary artery disease in the United States has increased from 7.9 per 100,000 in 1930 to 290 per 100,000 in 1963 (1). Significant progress has recently been made in the management of myocardial infarction with the introduction of Coronary Care Units, which aid greatly in the accuracy of diagnosis and in the prevention of lethal complications such as arrhythmias and congestive heart failure. However, the treatment of shock accompanying myocardial infarction, which ensues in approximately 10 to 20% of all cases, is still associated with mortality of 85 to 100% (2). This communication will emphasize a recent advance in the application of circulatory assistance to the critically ill patient with "pump failure."

The Dual-Chambered Intraaortic Balloon

When the single-chambered, omnidirectional intraaortic balloon pumps intraaortic blood, much of its effectiveness in supporting the coronary circulation in diastole is dissipated (Fig. 1). The unidirectional dual-chambered balloon which was developed in our laboratory pumps intraaortic blood entirely towards the aortic root in diastole, effecting a 66 to 100% greater increase in coronary blood flow over and above that obtained from a single-chambered balloon of equal displacement (3–7). The dual-chambered balloon has a spherical, slightly wider distal chamber which inflates early in diastole and occludes the aorta (Fig. 2). This is immediately followed by the inflation of a narrower cylindrical proximal chamber which pumps intraaortic blood entirely towards the aortic root. Both chambers are completely deflated by an active vacuum just prior to ventricular ejection. The balloon, which is fashioned from polyurethane, is mounted on a single-lumen, radio-opaque polyurethane catheter, and the sequential inflation and deflation of the two chambers is accomplished by the internal arrangement of the catheter coupled with a valve. In our clinical cases, the total displacement of the dual-chambered balloon used was 30 cc; the diameter of the occluding balloon was 18 mm, and the diameter of the pumping balloon was 14 mm, which was 3 to 4 mm less than the assumed aortic diameter. At the present time, we heparinize our patients with 1 mg per kilogram of intravenous heparin administered every 4 to 6 hours. However, our recent studies indicate that anticoagulation is probably not necessary. We have already successfully used the dual-chambered balloon as an aid in taking patients off total cardiopulmonary bypass after difficult valvular or revascularization procedures, despite protamine reversal of heparin.

From the Department of Surgery, Albert Einstein College of Medicine, 1300 Morris Park Ave., Bronx, N. Y. 10461.

* Developed by the Datascope Corporation, Saddle Brook, N. J.

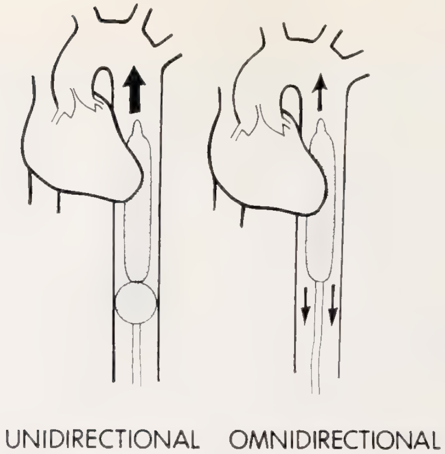

FIG. 1. Single versus Dual-Chambered Intraaortic Balloons.

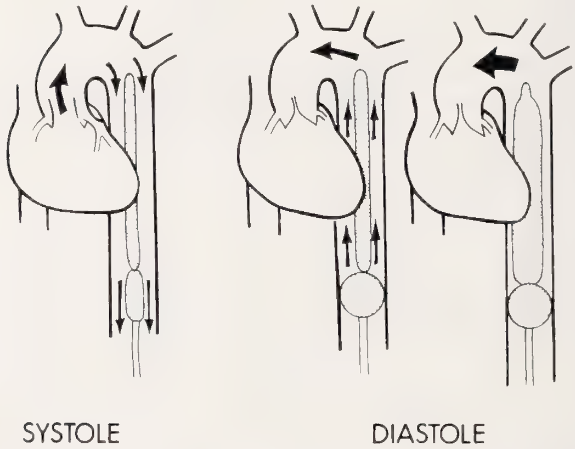

FIG. 2. Mechanism of Action—Dual-Chambered Intraaortic Balloon.

Counterpulsation

The concept of counterpulsation, which is the basis of intraaortic balloon pumping (IABP) was first described by Harken in 1958 (8), and, as originally proposed, consisted of the removal of blood via the femoral route from the arterial tree during ventricular systole and the rapid reinfusion of the same blood during diastole, to increase coronary perfusion pressure. By this method, in the normotensive preparation, one could decrease left ventricular work and increase coronary blood flow, thereby improving the balance between myocardial oxygen supply and oxygen demand (9). This method was initially received with great enthusiasm and several investigators have reported some success with its clinical application (10–13). However, the method as described has several drawbacks: 1) The excessive turbulence caused by the rapid withdrawal and reinfusion of the blood causes appreciable hemolysis, and therefore limits the duration of clinical applicability; 2) Either a bilateral femoral cut-down, or a subclavian arteriotomy is required for this procedure; 3) It has been shown by Dormandy et al (14) that when one counterpulsates via the femoral route in the hypotensive state there is no increase in coronary blood flow. Because of these drawbacks to the potential requirement for prolonged circulatory support, other investigators chose to apply the principle of counterpulsation in another unique fashion.

In 1961, Moulopoulos (15) suggested the use of a single-chambered intraaortic balloon placed in the descending thoracic aorta to accomplish the same purpose as counterpulsation without its drawbacks. The balloon is inflated in diastole beginning with closure of the aortic valve and is held in inflation until the onset of ventricular systole, when the balloon is rapidly deflated. The inflation of the balloon displaces intraaortic blood towards the coronary tree, augmenting coronary flow. The collapse of the balloon creates a "sink" which decreases left ventricular afterload and consequently reduces left ventricular work (16). After a hiatus of 7 years, Kantrowitz (17) reported the first successful clinical application of single-chambered intraaortic balloon pumping.

The main advantages of IABP over conventional arterio-arterial counterpulsation are that: 1) A single femoral arteriotomy is required. 2) Assistance is possible for extended periods of time since there is minimal hemolysis; 3) Coronary blood flow is augmented even in the hypotensive state (18).

Two additional significant advantages result from the use of either counterpulsation or IABP: 1) It has been demonstrated by Jacobey (19) that after a period of counterpulsation, dormant coronary collateral beds are opened and these channels remained open after the procedure terminated. 2) It has been demonstrated by Cox (20), Nachlas (21), and Sugg (22) that early institution of IABP or counterpulsation would decrease the size of the potential myocardial infarction after coronary occlusion.

The initial reports of single-chambered IABP seem promising (23–30), but the technique of application and the system used have several drawbacks which have recently been improved.

The Present Clinical System for Dual-Chambered IABP and Its Safety Features

The entire system for circulatory support utilizing the dual-chambered intraaortic balloon is now mounted on a single portable cart which can be battery operated. This has the advantage of mobility, and also enables one to transport the patient either from the operating room to the recovery room or from the Coronary Care Unit to the Angiographic Suite without any break in circulatory assistance. There are several safety features which are inherent in our present system and which, in our opinion, make it the safest and most reliable unit for clinical IABP. These safety features are as follows:

1. Balloon pumping is effected by utilizing an electronic control system in which the R-wave of the ECG triggers deflation of the intraaortic balloon* and is followed by inflation during diastole, thereby assuring that pump systole never coincides with ventricular systole (Fig. 3). Since the R-wave immediately deflates the intraaortic balloon, any ectopic or premature beat would also serve

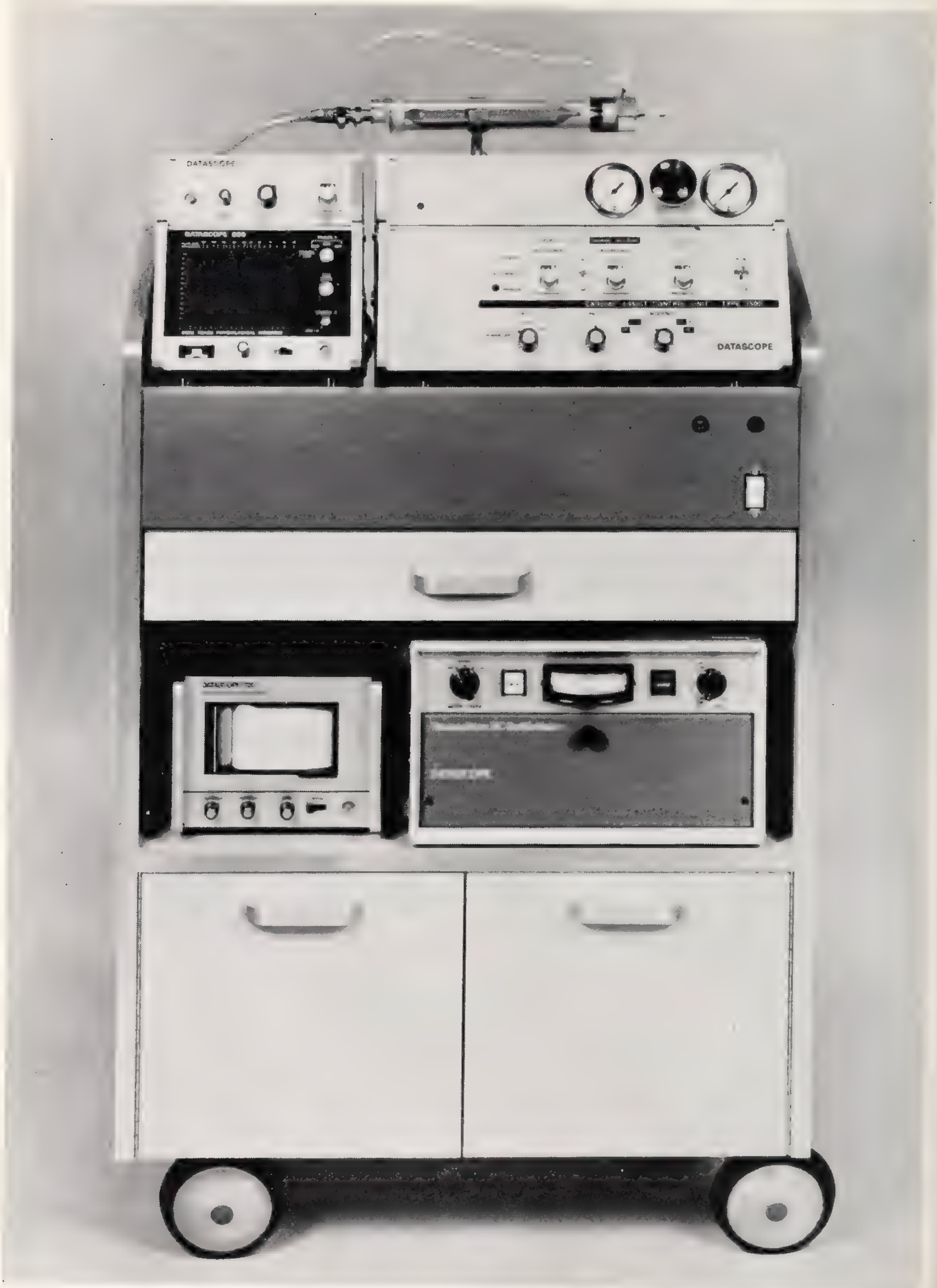
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Fig. 3. Battery-Operated Electronic Console for Intraaortic Balloon Pumping (Datascope System 80).

to deflate the balloon so that arrhythmias are not a problem in balloon pumping. As a point of clinical information, several patients with arrhythmias have been supported with the dual-chambered intraaortic balloon, and these arrhythmias rapidly clear in the first several minutes of circulatory assistance, probably as a result of the improvement of myocardial performance secondary to the increase in coronary perfusion and the decrease in ventricular work. If the patient has an extremely bizarre arrhythmia, a pacemaker is used without hesitation. Although the unit has a built-in automatic cutoff, an additional safety feature is now utilized in the event that an R-wave is not sensed. With the onset of systolic pressure, if the balloon has not already deflated, it will then do so. Additionally, if any electronic failure occurs, such as diminution of vacuum, the unit will automatically fail in exhaust.

2. A safety chamber, which is interposed between the gas supply and the intraaortic balloon, offers several clinical advantages (Fig. 4). In our closed system, the safety-chamber balloon which is precharged with 30 cc of carbon dioxide works in tandem with the intraaortic balloon, thus affording accurate visual control of the intraaortic balloon's performance in the aorta and assuring the complete expansion of the intraaortic balloon without any possibility of its

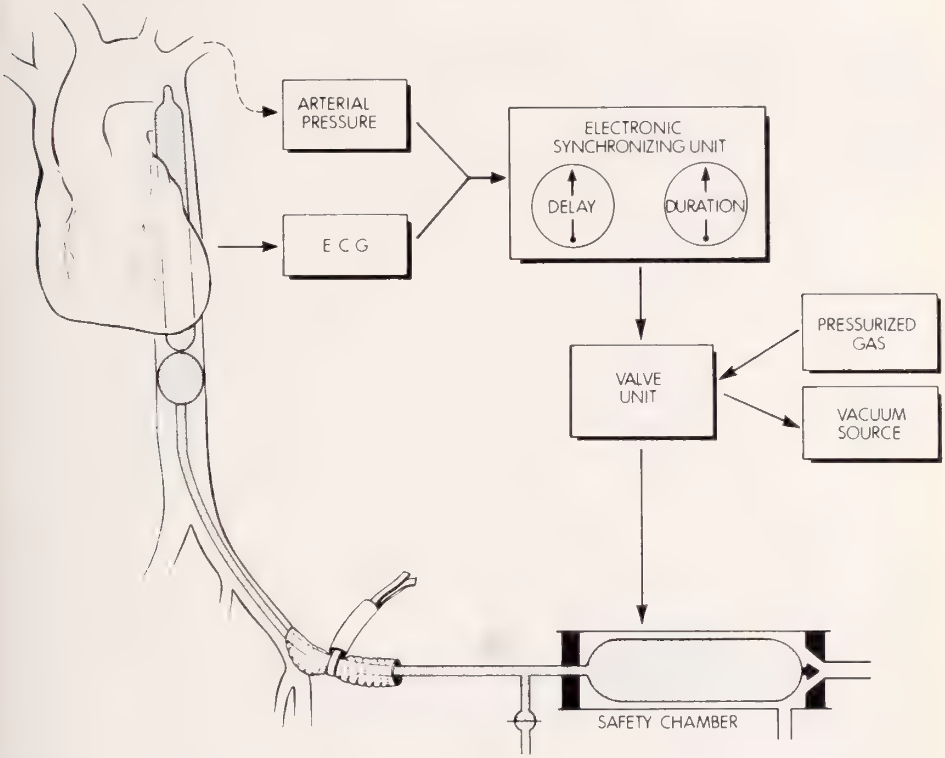

FIG. 4. Schematic Diagram of Dual-Chambered Intraaortic Balloon Pumping.

overdistension. If the intraaortic balloon should rupture, the patient would only receive a CO_2 bolus equal to the original safety chamber balloon charge.

3. As stated, the soluble gas carbon dioxide is used to effect IABP rather than helium, without any delay in gas transfer.

4. An appropriately timed vacuum applied to the safety chamber assures complete deflation of the intraaortic balloon with a maximum decrease in ventricular afterload and without any possibility that a partially inflated balloon could act as an obstruction in the aorta during a subsequent systole.

5. After the intraaortic balloon has been inserted and dual-chambered balloon pumping has commenced, a preclotted 10 mm dacron vascular graft, previously passed over the balloon catheter, is sutured to the femoral artery and is then snared to permit perfusion of the distal extremity during the period of cardiac assist (Fig. 4).

Laboratory and Clinical Experience

The dual-chambered intraaortic balloon has been tested extensively in the laboratory and found to be the most physiologically effective intraaortic balloon at the present time which is clinically applicable. Aside from the significant reduction in ventricular work, the dual-chambered balloon will increase coronary blood flow at least 66–100% greater than the increase obtained with a single-chambered balloon (3). The changes in renal blood flow below the dual-chambered balloon are not statistically significant. Should oliguria be a problem after the patient has become hemodynamically stable, the dual-chambered balloon can be lowered to a position in which the occluding balloon is below the renal orifices (4). This has the advantage of perfusing the kidneys both in systole and diastole.

Our criteria for patient selection in cardiogenic shock have been described elsewhere (4). At the present time we have evaluated and considered for circulatory assist 25 patients at the Bronx Municipal Hospital Center. These patients were treated with intensive medical therapy and it was elected to apply circulatory assistance in nine patients (Table I). All were refractory to medical therapy, eight were anuric, and four were comatose. In two of these patients with severe aortoiliac disease, the balloon could not be inserted and the patients expired within an hour of the attempts. Had these patients survived longer, a transaxillary approach would have been utilized with a modification of the dual-chambered intraaortic balloon. Of our six cardiogenic shock patients who were assisted for an average of seven hours, three survived pumping and were returned to the Coronary Care Unit. One patient (Case 2) expired from infarct extension after hemodynamic stabilization as a sequelae of dibenzylene administration. One patient (Case 3) succumbed two days postassist from pneumonia with renal failure. A third hemodynamically stable patient (Case 6) expired after the intravenous injection of Edecrin.® A fourth hemodynamically stable patient (Case 7) expired during the insertion of a pacemaker. There were two longer-term survivors and one patient has been alive and well for 1½ years. The four comatose patients awoke within 30 minutes. All were initially in

TABLE I

Clinical Experience—Dual-Chambered Intraaortic Balloon Pumping

Case	Age and sex	Previous infarcts	Interval from onset of infarction to onset of cardiogenic shock (hr)	Interval from onset of cardiogenic shock to initiation of assist (hr)	Cardiac arrests	Duration of assist (hr)	Course	Cause of death
1	63 M	1	1	53	5	4	Alive and well at 1½ years	—
2	76 M	0	60	36	0	16	Improved during assist, expired suddenly	Infarct extended into septum, acute heart failure, acute A-V dissociation
3	64 M	1	6	27	1	15	Survived 2 days	Pneumonia, renal failure
4	55 F	0	38	9	1	11	Survived and well for 7 days	Sudden death from ventricular rupture and tamponade
5	44 M	0	—*		0	14	Improved, transferred for aneurysmectomy	Inadequacy of left ventricular chamber
6	58 F	0	28	12	1	5	Stabilized during assist	Sudden expiration after IV Edecrin®
7	80 M	1	1	15	0	33	Stabilized during assist	Expired during insertion of pacemaker

* Myocardial infarction with intractable left ventricular failure for 2 weeks.

some degree of pulmonary edema, but within 30 minutes of assist all had clear chests. One additional terminal oliguric 44-year-old patient with intractable left ventricular failure two weeks postmyocardial infarction was successfully assisted for 14 hours. Pumping produced a prompt diuresis and the cardiac output rose from an initial 3.5 to 5.3 liters per minute. After angiograms were obtained during balloon pumping, open heart surgery was performed with the resection of an extensive left ventricular aneurysm.

Discussion and Perspective

The clinical application of dual-chambered IABP in our hands has proven to be a safe, effective, and rapidly instituted bedside procedure both for the acutely ill patient in cardiogenic shock (4–7), and as a supportive technique during cinecoronary angiography and ventriculography prior to definitive cardiac surgery (31). The primary beneficial effects of IABP are an increase in coronary blood flow and a decrease in left ventricular work. Clinical experience has failed to show that reducing left ventricular pressure work alone leads to a reduction in the mortality rate in patients with acute myocardial infarction and shock (32). However, when the depressed coronary blood flow is increased to more normal levels, ventricular function is improved and susceptibility to arrhythmias is reduced. The dual-chambered intraaortic balloon was specifically designed to maximally increase coronary blood flow. Although our clinical series is small, initial observations would tend to support the rationale for a unidirectional balloon since the total pumping time required in our patients for hemodynamic stability has been considerably shorter than the time required for stabilization of patients supported with a single-chambered omnidirectional balloon. The electronic and safety features built into our total system insure the minimum possibility of iatrogenic complications with a maximally effective support mechanism. The addition of a vacuum to the pumping system is particularly important since this makes collapse of the intraaortic balloon completely independent of the patient's intraaortic blood pressure (4–7). If a vacuum is not used, it is possible that the balloon would not completely deflate and that over a prolonged period the patient's ventricle would contract against a partially inflated balloon and would consequently increase left ventricular work and results in a ruptured myocardium. This has been seen clinically in several patients in whom single-chambered balloon support has been applied without the use of a vacuum (24). The use of carbon dioxide instead of helium is a significant advance since helium is quite insoluble in blood and since there have been several cases of clinical balloon rupture with the use of helium by other investigators, with the resultant rapid demise of the patient (27, 33). The timing of the intraaortic balloon is accomplished by a few simple manipulations on the pumping console, and the stability of the unit has been quite apparent to us since only minor adjustments are occasionally required over several hours. Our experience has shown us that a transvenous pacemaker should probably be inserted prior to assist and that the use of dibenzylene and Edecrin® may be detrimental.

The Future of Circulatory Assistance

With the current trend towards the use of noninvasive techniques, two other applications of clinical counterpulsation have emerged: 1) Synchronous Pressure Assist Counterpulsation (34), and 2) Body Acceleration Synchronous with the Heart Beat (BASH) (35). Both of these methods are currently under preliminary clinical investigation, but it appears that their primary benefit would be in patients who are not in shock but who would be counterpulsated for less demanding conditions such as intractable failure or intractable angina pectoris.

There will continue to be patients who can be successfully supported by an intraaortic balloon device, but who will reach a plateau of stability and then are unable to be weaned from intraaortic balloon assistance. It is our present feeling that if a patient cannot be weaned from continuous balloon support within 24 hours, he should then be taken to the Angiography Suite, studied with cinecoronary angiography and ventriculography, and have definitive open-heart surgery performed on the basis of the radiographic findings. We also advocate angiographic study of patients surviving circulatory assistance since, in our own experience, a patient expired one week postassist from what was probably a preexisting, surgically correctable myocardial lesion. In conjunction with saphenous vein revascularization, and the resection of ischemic and noncontractile segments or ventricular aneurysms, it is anticipated that many patients who were formerly unsalvagable will now be brought to the operating room for definitive cardiac surgery in a more viable state. Aside from its primary use in cardiogenic shock, the intraaortic balloon will find its use in patients with intractable angina pectoris or with preinfarction angina. In addition, patients with intractable left ventricular failure will now be able to be supported, improved, studied, and then evaluated for possible surgery. When the immunologic barriers to cardiac transplantation have been solved, acutely ill patients will be able to be supported with this mode of circulatory assistance and then will be brought to the OR for cardiac transplants, or eventually for replacement with a total artificial heart. Also on the horizon is the use of the dual-chambered intraaortic balloon as an aid in neurosurgery. There are several neurosurgical conditions which result in cerebral vasospasm (such as in the immediate period following the surgical clipping of a cerebral aneurysm). In these conditions, the increase in cerebral blood flow may prove to be beneficial to the preservation of cerebral matter and the eventual salvage of the patient. It is anticipated that as the technique of dual-chambered IABP becomes more widely accepted and the indications for its use become more clearly defined, it will be used earlier to break the vicious cycle of cardiogenic shock so that clinical results of this encouraging mechanical assist technique will more accurately reflect *survival* rather than *salvage* figures.

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Intrathecal Injection of Isotonic Iced Saline for Intractable Pain

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Introduction

The search for a safe and dependable method for the alleviation of chronic and intractable pain is a continuing one. Particularly in terminal carcinoma, pain relief may be the most important part of therapy, both to the patient and the family. Unfortunately, no analgesia program yet available consistently gives sustained relief or permits normal function. The future may bring development of the perfect nonnarcotic analgesic without side effects. Until then, the nervous system will have to be insulted in the gentlest manner which can alleviate pain with the least other neural injury.

Neurosurgery in the form of cordotomy or rhizotomy or even frontal leukotomy has been applied, and more recently, the dorsal column stimulation technique. Nerve blocks, as well as subarachnoid alcohol or phenol injections, have also been used extensively. All of these methods share the disadvantages of more or less major interventions on a group of patients usually in poor condition with limited life expectancy. There is in addition the problem of a significant complication rate and an appreciable failure rate.

The effects of hypothermia on the nervous system and perfusion of the subarachnoid space have been studied for many years. Hitchcock (1) introduced hypothermic subarachnoid irrigation for the relief of intractable pain and subsequently inquired into the hyperosmolarity of his solution. Ensuing clinical research explored the use of anesthesia, increasingly hypertonic saline, prolonged irrigation, elaborate perfusion apparatus, and varying sites of injection. To our knowledge, no previous investigators have reported the primary results of brief, isotonic, hypothermic spinal irrigation.

Materials and Method

The irrigating solution was prepared by keeping 500 cc IV bottles of normal saline in a regular refrigerator freezer just until ordinary ice cubes formed. During the procedure, a small bucket filled with crushed ice maintained the temperature in the bottle between 0° and −1° C without crystallization. Analysis of our iced saline failed to reveal any increase in osmolarity: 308 mOsm/L, consisting of 154 meq/L sodium and 154 meq/L chloride.

The patient was placed on a tilting table in the lateral position. After sterile prepping and draping and infiltration with a local anesthetic, lumbar puncture was performed with a #16-gauge spinal needle. Placement within the spinal

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canal was evaluated by the quality and quantity of flow. After recording the initial pressure and checking the manometrics, cerebrospinal fluid was allowed to flow out spontaneously until subambient pressure was produced. Mechanical withdrawal by syringe was specifically avoided to prevent aspiration of a nerve root or alteration of the needle tip within the subarachnoid space.

If the cerebrospinal fluid was grossly hemorrhagic and did not clear, the procedure was discontinued. If the patient reported any sign of cauda equina irritation, the needle placement was revised. Increased intracranial pressure or spinal block was not encountered in our series, but either would have been considered a contraindication to continuing and an indication for further study.

When the pain was unilateral, the patient remained with the affected side down. When the pain was bilateral or midline, the patient was positioned prone. The table was then tilted from −60° to +60°, so that the appropriate area could be adequately irrigated.

A second ✻16-gauge needle was intermittently attached to a 12 cc syringe for sterile aspiration of the hypothermic solution from the supply bottle. Repetitive injections were performed as rapidly as possible to produce maximum cumulative cooling. Between injections, the spinal needle was left open; and the free back-flow allowed for continuous evaluation of needle placement as well as prevention of pressure build-up. After the final 12 cc injection, back-flow was not permitted; and the needle was removed.

With the use of only local Xylocaine®, there was severe subjective experience of paresthesias and fasciculations which interfered with rapid, repetitive irrigation and dissuaded patients from allowing subsequent cooling. Various hypnotic-sedative, tranquilizing, neuroleptic, and anesthetic agents were therefore administered. A combination of Innovar® 1–2 cc and either Surital® 100–200 mg or Valium® 10–20 mg, given intravenously just prior to the period of actual perfusion, was found to effectively reduce the discomfort while allowing evaluation of regional muscle contractions. At this light plane of anesthesia, a total of 72 cc of iced saline could regularly be employed for lower quadrant pain, and 96 cc for upper quadrant pain. One patient, because of radiation fibrosis of the lungs and allergy to local anesthetics, underwent general endotracheal anesthesia with nitrous oxide; another patient elected to undergo Pontocaine® spinal anesthesia.

Fasciculations were limited to the period of actual cooling, while dysesthesias continued in some of our patients up to two hours and not infrequently required additional medication. All patients reported at least transient analgesia following the procedure. Hypesthesia was often noted in the affected area for periods up to forty-eight hours. Cephalgia and local discomfort from spinal tap occasionally required minor analgesics. Two patients with preexisting lower extremity weakness, secondary in one case to know myelopathy and in the other to suspected radiculopathy, experienced a temporary increase in paresis for several days.

Following irrigation, relief was frequently described as complete cessation of intractable pain, but also in terms of aching or stiffness easily alleviated by

SUMMARY OF

case	age sex	diagnosis	presenting problem	
1	71 F	metastatic carcinoma of uterus	A	intermittent, severe pain in low back and LLE; confined to bed
			B	unremitting pain in pelvis and RLE; confined to bed; cachexia
2	78 M	metastatic carcinoma of rectum S/P colostomy	A	constant aching in low back and RLE; pain when lying on right side or walking
3	38 F	metastatic carcinoma of breast	A	constant pain in RUE; unable to use dominant hand
			B	unremitting burning in pelvis; confined to bed
			C	stabbing pain on moving LUE; pathologic fracture of left humerus
4	62 F	metastatic carcinoma of rectum S/P colostomy	A	constant burning in perineum; confined to bed; cachexia
5	74 F	causalgia, S/P sympathectomies peripheral vascular disease	A	severe burning in plantae on stroking of shins; unable to walk comfortably
6	50 F	post-herpetic neuralgia S/P LUQ laparotomy	A	constant burning in left T10 dermatome; uncomfortable during normal activity
7	64 F	S/P laminectomy and excision of HNP intractable low back pain	A	intermittent burning in rectum and both thighs; pain when walking
8	46 M	metastatic carcinoma of rectum S/P colostomy	A	unremitting, severe pain in low back and left buttock; confined to bed
9	60 F	metastatic carcinoma of cervix	A	constant aching in low back and RLE; confined to bed
10	21 F	S/P excision of left knee hemangioma causalgia	A	severe burning in left knee triggered by stroking thigh; pain when walking
11	66 F	metastatic carcinoma of vulva	A	unremitting pain in both thighs and pelvis; confined to bed
12	53 F	Pancoast syndrome	A	constant burning in neck and RUE; intense pain when using dominant hand
13	52 M	metastatic carcinoma of rectum S/P colostomy, S/P cordotomy	A	intermittent aching in low back and both thighs; pain when walking; weakness in LLE
14	42 F	metastatic carcinoma of breast S/P right mastectomy	A	unremitting, severe pain in neck and both shoulders; confined to bed
15	37 F	S/P laminectomy and excision of HNP intractable low back pain	A	intermittent pain in buttocks radiating down both posterior thighs
16	49 F	metastatic carcinoma of breast S/P left mastectomy	A	intense pain in neck and left shoulder; confined to bed
17	70 F	intercostal neuralgia S/P left thoracotomy	A	intermittent burning in left T8 distribution; pain when sitting
18	51 F	S/P laminectomy, low back pain mitral stenosis, S/P cordotomy	A	intermittent painful spasm in low back; angina pectoris; confined to bed
19	53 F	S/P laminectomy and excision of HNP intractable low back pain	A	constant aching in low back; pain during normal activity
20	79 F	S/P hiatus hernia repair post-herpetic neuralgia	A	constant burning in left T10 dermatome; uncomfortable during normal activity
21	59 F	metastatic carcinoma of breast radiation fibrosis of lungs	A	unremitting pain in right thorax; dyspnea at rest; confined to bed
22	36 F	metastatic carcinoma of colon right L4 radiculopathy	A	constant aching in buttocks and LLE; pain when walking; weakness in RLE
23	55 F	metastatic carcinoma of breast S/P mastectomies	A	intermittent pain in entire thorax; confined to bed
24	52 M	intractable pain in buttocks S/P coccygectomy	A	constant aching in both buttocks; unable to sit or walk comfortably
25	49 F	metastatic carcinoma of breast S/P mastectomies, S/P adrenalectomies	A	intense pain in both legs; unable to walk comfortably
			B	intermittent pain in both shoulders and thorax; unable to use arms
26	47 F	metastatic carcinoma of breast S/P right mastectomy	A	unremitting, severe pain in lower thorax and abdomen; confined to bed

medication. In addition to the patient's subjective evaluation, some objective appraisal of pain relief was possible by observing: 1) self-imposed reduction of medication, 2) mood elevation, and 3) return in part or whole to a functional life-style. The patients who were afforded relief from unrelenting pain readily reduced their analgesics and narcotics without withdrawal symptoms almost

CLINICAL DATA

position	site	amount	clinical result	relief
left side +45° tilt	L4-5	36 cc *	mood elevated; OOB AD LIB; nursing home transfer; occasional arthritis in LLE	3 months
right side +45° tilt	L4-5	72 cc	free of pain; appetite improved; able to sit up for brief periods	2 weeks coma/death
right side +45° tilt	L3-4	60 cc *	OOB with minimal discomfort;percutaneous cordotomy;dissatisfied with results	______
right side -45° tilt	L4-5	48 cc *	able to use right hand in comfort;evolving metastases	
prone +30° tilt	L4-5	72 cc	OOB to chair;unable to reduce medication sufficiently;evolving metastases	
left side -45° tilt	L4-5	96 cc	mood elevated;occasional pain when using LUE;discharged 3 days later	1 month coma/death
prone +30° tilt	L4-5	72 cc X 2	mood elevated; OOB AD LIB; discharged 3 days later	8 months coma/death
prone +45° tilt	L4-5	72 cc	able to walk without pain for 4 weeks; partial return of discomfort	1 month
left side -15° tilt	L1-2	96 cc X 2	essentially no relief	______
prone +30° tilt	L1-2	72 cc	less discomfort when sitting or walking; dissatisfied with result	______
left side +30° tilt	L4-5	72 cc	able to sit and walk without pain for 8 weeks; partial return of discomfort	2 months coma/death
right side +45° tilt	L3-4	72 cc	mood elevated; appetite improved; OOB to chair; nursing home transfer	4 months coma/death
left side +30° tilt	L4-5	72 cc	able to walk without pain for 4 weeks; partial return of discomfort	1 month
prone +30° tilt	L3-4	72 cc	mood elevated; appetite improved; able to sit up comfortably	2 weeks coma/death
right side -60° tilt	L3-4	96 cc X 3	full range of motion in RUE; rhizotomy; unable to reduce medication	______
prone +45° tilt	L3-4	72 cc X 2	no discomfort for 8 weeks;partial return of pain;chemotherapy/radiotherapy	2 months
prone -60° tilt	L3-4	96 cc X 2	mood elevated; OOB to chair; occasional neck stiffness; nursing home transfer	1 month coma/death
prone +45° tilt	L1-2	72 cc	mood elevated;mild paresthesias when exercising;discharged 3 days later	6 months to date
left side -45° tilt	L2-3	96 cc X 2	mood elevated; full range of motion in LUE; chemotherapy/radiotherapy	4 months coma/death
left side -30° tilt	L3-4	96 cc	no relief; unsuccessful rhizotomy	______
prone +30° tilt	L1-2	72 cc X 2	decreased low back pain and angina; increased activity; medication unchanged	______
prone +30° tilt	L1-2	72 cc	minimal discomfort in low back when exercising; discharged 2 days later	6 months to date
left side -15° tilt	L1-2	96 cc X 2	essentially no relief	______
right side -30° tilt	L3-4	96 cc	mood elevated; OOB to chair; no further pain	8 days PE/death
left side +60° tilt	L3-4	72 cc	transient increase in paresis;no further pain;unable to reduce medication	______
prone -30° tilt	L3-4	96 cc	mood elevated;OOB AD LIB;partial return of pain at 8 weeks;radiotherapy	2 months
prone +15° tilt	L1-2	72 cc X 2	occasional low back discomfort;increased activity;discharged 4 days later	6 months to date
prone +45° tilt	L3-4	72 cc X 2	able to walk without discomfort;evolving metastases	
prone -45° tilt	L3-4	96 cc X 2	mood elevated; moderate stiffness in all limbs; partial return of pain at 8 weeks	2 months
prone -15° tilt	L2-3	96 cc	no discomfort for 8 weeks;partial return of original pain	2 months

*no anesthesia

immediately after the procedure. Despite transitory variations, the sustained affective state of such patients remained elevated. Finally, those patients who had been bedridden and demoralized and cachectic were often able to go home and resume family and social life. Unless these three observations were made, the procedure was not deemed successful, even if the range of motion in an affected limb or the overall physical activity of the patient or the response to placebo medication improved.

If the relief from pain was incomplete or less than forty-eight hours in duration, the entire procedure was repeated once, and in one case twice. If multiple areas of the body were involved with diffuse metastases, different levels were serially irrigated. In two patients, the entire spinal cord was irrigated by three separate procedures in one and four separate procedures in the other.

Results

Forty-two separate irrigations with isotonic iced saline were performed on twenty-six patients—sixteen metastatic neoplasms, four discogenic low back pain persisting after laminectomy, three neuralgia, two causalgia, and one buttock pain following coccygectomy. In effect, eighteen cases of lower quadrant pain and twelve cases of upper quadrant pain were treated in our initial series. Nine carcinoma patients obtained complete relief from intractable pain until death eight days to eight months later, four others had almost total relief for eight weeks before return of the original pain, and the remaining three had an equivocal result. Both causalgia patients were free of symptoms for one month before the return of some discomfort in the affected area; neither one was motivated toward repeat irrigation. Essentially no relief was produced in the two postherpetic neuralgia patients or the one postthoracotomy intercostal neuralgia patient. Two patients with discogenic postlaminectomy pain have improved up to six months to date, while the other two had an equivocal result. The patient with intractable buttock pain has obtained significant relief for six months to date. Of the patients whose pain was inadequately alleviated by hypothermic subarachnoid irrigation, two failed to acquire subsequent relief from rhizotomy, and one was no better after percutaneous cordotomy.

Successful Result: Case 3, a 38-year-old woman with known metastatic carcinoma of the breast, developed intractable pain first in her right shoulder and upper arm and was unable to use her dominant hand, then in her pelvis and low back and was confined to bed, and finally in her left neck and shoulder and could not reduce her medication requirement. Following the first irrigation, she regained full use of her right upper extremity; with the second irrigation, she was able to sit without discomfort; after the third irrigation, her mood elevated, her dependence on narcotics decreased, and despite a pathologic fracture of the left humerus she was able to go home where she remained until her sudden deterioration and death one month later.

Successful Result: Case 10, a 21-year-old woman who had undergone excision of a hemangioma of the left knee, developed causalgia triggered by stroking the medial aspect of the thigh. For one month following spinal cooling, she was able to walk without her clothes triggering the causalgia. She presently has intermittent discomfort in her left knee, relieved by minor analgesics, and has not requested further irrigation to date.

Unsuccessful Result: Case 6, a 50-year-old woman who had undergone a laparotomy for regional ileitis, developed postherpetic neuralgia in her left T10 dermatome. She described her pain as a constant burning which made all normal activity uncomfortable. After two separate irrigations, her neuralgia was essentially unchanged.

Unsuccessful Result: Case 17, a 70-year-old woman who had undergone thoracotomy for a hiatus hernia repair, developed intercostal neuralgia involving the left T8 distribution. She described her pain as constant burning under her left breast. Intrathecal iced saline produced no lasting results. Following rhizotomy at levels T6, 7, 8, 9, she still complained of her original pain in spite of permanent hypesthesia to pinprick in the dermatomes of the severed nerve roots.

Equivocal Result: Case 2, a 78-year-old man with known metastatic carcinoma of the rectum, developed constant aching in his low back and right lower extremity and could not lie on his side or walk without pain. After irrigation, his medication requirement decreased, straight leg raising improved from 15° to 80°, and he was able to walk with some discomfort in his right thigh. He elected to undergo percutaneous cordotomy, but remained dissatisfied with the overall results of both procedures.

Equivocal Result: Case 18, a 50-year old woman who underwent laminectomy and excision of a ruptured intervertebral disc, had a recurrence of low back pain about one year postoperatively. Arteriosclerotic heart disease made her a poor candidate for any further major surgery, and she undewent percutaneous cordotomy with good relief for five years. She presently complained of angina pectoris in addition to severe low back pain. Subsequent to two separate spinal coolings, she experienced decreased frequency of angina pectoris and diminished low back pain and was able to increase her daily activity; however, her medication requirement remained unchanged.

No permanent sensory deficits, bladder dysfunctions, or other complications directly attributable to hypothermia have been observed to date in our series of forty-two irrigations. Nevertheless, complications have been reported by other researchers, especially with the use of hypertonic saline; transient changes in blood pressure (2) and cardiac arrhythmias (3) have been attributed to direct stimulation of sympathetic fibers by lumbar injection or parasympathetic fibers by cisternal injection. O'Higgins (4) published one complication of left middle cerebral artery infarction. Hitchcock (2) related one complication of permanent cauda equina lesion.

Review of the World Literature

This program was stimulated by the work of Hoessly and Hakuba (5) at the Boston Veterans Administration Hospital, who treated a small number of patients with intractable pain by spinal cooling as originally described by Hitchcock. The patients were positioned with the involved side down. Following routine lumbar puncture, cerebrospinal fluid was withdrawn till subatmospheric pressure was produced. The table was then tilted to bring the affected part below the level of puncture. Aliquots of 10 cc of the supernatant from melting, frozen physiological saline were injected up to six times or until the patient reported cessation of pain. While analgesia lasting minutes to hours could be produced, variable lengths of sustained pain relief were obtained up to months in duration.

In May 1967, Hitchcock (1) published his first series of hypothermic hyperosmolar subarachnoid irrigations—one group of nine patients with metastatic tumors, and a second group of three patients with various central nervous system lesions. Worthwhile relief up to three months was obtained in seven of the first group, whereas no palliation was produced in the latter group. In June 1967, Hitchcock (6) elaborated on his original paper by raising the possibility that the hyperosmolarity of his irrigating solution might alone have produced the beneficial effect. In March 1969, he reported a series of seven patients with facial carcinomas treated by cisternal injection of hypertonic saline (7). Up to 20 cc of saline solution was used with temperatures ranging from 4° to 36° C and osmolarities ranging from 598 to 3000 mOsm/L. The patients commonly showed transient facial weakness, vertigo, nystagmus, emesis, and bradycardia. The pain relief was immediate, but variable in duration from three days to three months. In April 1970, he further reported that he had ceased irrigating with hypothermic solutions, preferring the more easily prepared and more readily controlled hypertonic solutions (2).

Negrin (8, 9) has used various physiological solutions at temperatures ranging down to 5° C to treat muscular rigidity and spasticity and to protect the spinal cord against the effects of trauma. Local hypothermia of the central nervous system was accomplished by surgically placed, indwelling catheters. Irrigation was prolonged by a specially developed perfusion machine, which has been used more recently to treat refractory seizures and intractable pain.

In January 1968, Nicholson and Roberts (10) first described the use of general anesthesia in four metastatic carcinoma patients treated with intrathecal iced saline. The theoretical advantage of assessing the exact amount of irrigation required to effect analgesia was far outweighed by alleviation of the paresthesias and fasciculations accompanying the procedure. Three out of four patients treated with 40 cc irrigation obtained significant relief up to one month.

In March 1969, Collins et al (11) reported a series of twenty cases with intractable pain—nine causalgia, three postherpetic neuralgia, four metastatic tumors, one pancreatitis, one bilateral AK amputation, one Buerger's disease, and one peripheral arteriosclerosis. With the patient in extreme Trendelenberg's position, he irrigated through a #17-gauge Tuohy needle partially frozen saline (specific gravity 1.006), equal in volume to the cerebrospinal fluid withdrawn in producing subambient pressure. The procedure was performed at times with an intravenous thiopental drip, and also in combination with sympathetic blocks. Evaluation was conducted by asking the patient, "If the pain was 100 percent before the block, what is it now?" Excellent results (0 to 25 percent) were described in the causalgia patients, good (50 percent) to excellent in the neuralgia patients, and fair (75 percent) in the remainder during a one year follow-up.

In June 1969, Tsubokowa (12) published ten cases of intractable pain: seven metastatic carcinomas, one fracture of lumbar vertebra, one phantom limb pain, and one ruptured intervertebral disc. The patient was placed in the lateral position with the affected side beneath and the upper part of the body raised 10° to 20°. The injection site was one or two interspaces cephalad to the segment of spinal cord involved. The total perfusion volume was 20 cc over the withdrawal volume, with the temperature ranging from −2° to +2° C and the sodium/chloride concentration ranging from 160 to 200 meq/L. In order to reduce the discomfort of paresthesias and fasciculations, only 3 to 5 cc was injected at two- to four-minute intervals. The original pain recurred to a lesser extent within one week; and the interval method of perfusion was repeated once or twice within ten days, with subsequent relief lasting from twenty to forty days. The one patient who obtained no significant relief was noted to have a spinal block.

Mathews' (13) earlier work with Pace-Floridia appeared in November 1970; four out of seven patients with intractable pain due to terminal carcinoma obtained satisfactory relief from three weeks to four months following hypothermic subarachnoid irrigation as originally described by Hitchcock. Mathews' (14) later research with Ambruso and Osterholm appeared in October 1970 with a report on eight cases—six metastatic carcinomas and two nonneoplastic painful syndromes. With the patient in the sitting position, a #18-gauge spinal needle was inserted into the cisterna magna, and a vented #20-gauge spinal needle into the lumbar subarachnoid space. Valium®, 10 to 30 mg, was administered intravenously just prior to cisternal injection of 30 to 50 cc of saline cooled to the point of crystallization (400 to 500 mOsm/L). Body tilting, nystagmus, fasciculations of face and arm muscles, bradypnea, and transient dysarthria were regularly observed. Four of the metastatic neoplasm patients had almost total pain relief until death one to three months later, while two obtained transient relief from five to seven days until a recrudescence of symptoms.

Discussion

Perl and coauthors (15, 16, 17) presented considerable evidence in favor of the concept that sense organs of the skin with unmyelinated C fibers have widely varying functional characteristics. In the mammal, a large proportion of such sensory units were excited by gentle mechanical stimuli and by transient cooling; a second group responded best to small temperature changes; and a third group had elevated thresholds for various or all stimuli. The intensity of the liminal stimulus and unique ability to provide signals marking the difference between innocuous, threatening, or overly damaging stimuli strongly indicated a nociceptive function for the high-threshold, unmyelinated sensory units. The sensitization of polymodal nociceptors following noxious heat simulated certain kinds of hyperalgesia. Furthermore, the pericornual cells of Rexed's lamina 1 could be antidromically fired by stimulation of the opposite anterior lateral funiculus in the cervical area, demonstrating the absence of internuncial cells and the dispensability of the modulation concept inherent in the gate control theory (18, 19).

Studies on the effects of temperature and osmolarity on neural conduction have been contradictory. In 1945, Denny-Brown and associates (20) observed that the myelin sheath of mammalian peripheral nerves is selectively damaged by exposure to cold and that complete regeneration occurs in all grades of injury short of complete necrosis. In 1947, von Euler (21) suggested that unmyelinated C fibers were more susceptible to cooling than thickly myelinated fibers, which might even be stimulated. In 1948, Lundberg (22) reported conversely that the conduction of A fibers ceased at 7° to 15° C in the cat, whereas conduction of splenic C fibers continued at 0° C in the cat and cow.

In 1957, Meyer and Hunter (23) measured the changes in size of monkey cortical veins and arteries during surface cooling and found reduction in vessel caliber beginning at 32° C. The change was most evident in arterioles with a diameter of approximately 200 millimicrons. Arterial size was estimated at 50 percent of normal, and the veins were reduced 25 percent at 30° C. At lower temperatures, the capillary beds appeared pale and poorly defined. Asphyxia of nerve trunks in animal experiments by Douglas and Ritchie (24) was found to block transmission in medullated fibers more readily than in nonmedullated fibers.

In 1958, Robertson (25) studied the structural alterations of frog nerve fibers produced by hypotonic and hypertonic solutions. Electron microscopy revealed that, while ice-cold distilled water could produce extreme distortions in some unmyelinated fibers, only splitting of the intraperiod lines was observed in myelinated fibers. Myelinated fibers exposed to hypertonic Ringer's solution exhibited no specific change, but distinct closure of the mesaxon gap occurred in unmyelinated fibers.

In a series of journal articles beginning in 1961, Albin (26, 27, 28), with various coworkers, investigated the results of sustained perfusion cooling of the subarachnoid space in dogs and first speculated whether hypothermia exerted a central anesthetic effect. The spinal cords were maintained at mean temperatures as low as 5.86° C for four hours without any neurological sequelae and with little histopathologic evidence of damage. In 1967, Albin et al (29) confirmed the earlier observations of Brooks and associates (30) and Suda and coworkers (31), that the action of cold on nerve conduction was opposite to that of local anesthetic agents—the larger the cross-sectional diameter of the fibers, the more sensitivity to hypothermia. Sensory blockade was achieved at a mean spinal cord temperature of 13.2° C, as demonstrated by the disappearance of an evoked cortical response upon contralateral sciatic stimulation. In a guest discussion of Albin's paper, Haugen raised the possibility that cord cooling might reduce afferent activity in the interneurons responsible for a vicious circle of reflex activity in chronic pain.

In 1971, Jewett and King (32) described a persistent conduction block in isolated monkey dorsal rootlets exposed to hypertonic saline for fifteen minutes. The block was detected primarily in C fibers with the use of hyperosmolar saline (500 to 2500 mOsm/L) and persisted at five hours after return of isotonicity. Few A fibers were blocked until the osmolarity was increased to 3500 mOsm/L. Differential blockage of C fibers could also be produced by hypotonic saline (0 to 200 mOsm/L). Cooling the dorsal rootlets to 2° C for twenty-five minutes created a conduction block of all the fibers, which disappeared within two minutes after rewarming to 38° C. Moreover, cooling did not potentiate the results of hyperosmolar solutions. Hypertonic solutions of sucrose or sodium nitrate caused no disruption of nerve conduction; however, choline chloride solutions were as effective as sodium chloride in establishing a conduction block. Therefore, an osmolar gradient of chloride ion was proposed as the mechanism of differential C fiber blockade.

Laboratory research into the mechanism of pain relief has been extensive but inconclusive to date. No animal model has been designed, which adequately simulates the complex human experience of intractable pain. The effects which have been documented are either transient phenomena or the results of extremes of temperature and osmolarity not attained in the clinical situation.

Only Tsubokawa (33) has made a comparative study of A-delta and C fiber conduction block with appropriate cooling and without appreciable alteration of osmolarity. Cat spinal cords were irrigated at L6-7 with 80 cc of iced saline (314 to 376 mOsm/L) over a fifteen-minute period. The temperature at the injection site was 7° to 8° C, and 8° to 10° C two segments away. Immediately after perfusion, the action potentials of A-delta and C fibers in the L6 dorsal root that were previously evoked by sciatic stimulation disappeared completely, while the action potentials of A-alpha and A-beta fibers were essentially unchanged; action potentials also disappeared in the mesencephalic reticular formation and the centromedian nucleus of the thalamus, but could still be evoked in the venteroposterolateral nucleus. Six hours after irrigation, action potentials did not reappear in the A-delta and C fibers or the mesencephalic reticular formation and the centromedian nucleus of the thalamus. Five to seven days after two separate spinal coolings, 60% of the prepared cats failed to exhibit evoked action potentials in the mesencephalic reticular formation or the centromedian nucleus of the thalamus following noxious stimulation of the sciatic nerve.

Postmortem examination of one patient in our series failed to reveal any demonstrable neurolysis of the spinal cord or nerve roots. Mathews (14) also reported no histologic changes in the medulla, spinal cord, or nerve roots of one patient who was autopsied. Hitchcock (1), on the other hand, reported widespread vacuolization and pallor of myelin staining in one patient who came to necropsy.

Patients with successful relief of their intractable pain after spinal cord cooling still have appropriate perception of pin prick, skin pinching, and deep pressure and can correctly identify a hot or cold stimulus. This observation indicates that at least the crude reaction to noxious stimuli or temperature is present. Careful testing for threshold differences has not been carried out, yet the relief of intractable pain is in clear contrast to the apparent preservation of response to painful test stimuli.

Initial fasciculations and paresthesias may be explained by transient activation of the larger A fibers in ventral and dorsal roots; successive hypesthesia may be caused by inactivation of the sodium pump for a limited period of time. Sustained pain relief may be attributed to cold trauma to a critical number of A-delta and C fibers or pericornual cells and their ascending axons. Alternatively, gate modulation could be rendered inoperative by damage to a still undemonstrated anatomical substrate of interneurons. The exact role of spinal cord ischemia secondary to vasospasm of the intrinsic vasculature remains undetermined. Further experimentation is necessary to ascertain whether the alleviation of pain is due to deactivation of peripheral fibers or prolonged quiescence of central internuncials.

Conclusions

Brief subarachnoid perfusion with isotonic iced saline under general anesthesia appears useful in the treatment of intractable pain. Twenty-six patients were treated by an evolved method of irrigation, designed to enhance the effects of hypothermia while avoiding the complications associated with hyperosmolar solutions. For the cases of terminal carcinoma and others considered poor surgical risks, the empirical results have been extremely satisfactory to the point of replacing cordotomy. For nonneoplastic painful syndromes, where neurosurgical intervention or reexploration is rarely indicated, spinal cooling offers an alternative therapeutic approach. The procedure has been helpful in the causalgias, moderately beneficial in discogenic postlaminectomy pain, and valueless in the neuralgias.

The technique described herein is simple, requires no special equipment, and is apparently without significant morbidity. Other forms of treatment, such as radiotherapy, chemotherapy, and physiotherapy, may readily be employed in combination. In the event of failure, there has been no interference with a more formal surgical procedure. Our data suggest that any patient considered as a candidate for pain-relieving neurosurgery should first undergo intrathecal injection of isotonic iced saline.

Acknowledgements

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Respiratory and Circulatory Effects of Pentazocine and Meperidine on Anesthetized Patients

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Pentazocine is a weak morphine antagonist of the benzomorphan series which, in the injectable form, has an analgesic action comparable to that of the opiates (1–3). Fraser and Rosenberg (4) showed that pentazocine had minimal abuse liability and in 1966 the World Health Organization (5) recommended that there was no need for national or international narcotic control; and a leading article in the Lancet (1967) (6) drew attention to the therapeutic importance of the drug.

The respiratory and circulatory effects of opiate drugs and their derivatives are well known. In analgesic doses to unmedicated, conscious patients it is very difficult to detect minor changes in respiration and hemodynamics unless complicated methods are used. Under general anesthesia, however, respiratory and circulatory depression is much more marked, and consistent changes can be obtained with relatively low dosage. This fact has been used to compare and contrast the cardio-respiratory effects of an initial and subsequent dose of pentazocine or meperidine in anesthetized patients.

A comparative study was undertaken involving three groups of 6 patients and one group of 7 patients. All were fit females undergoing minor gynecologic surgery, and all gave informed consent to the investigation.

The methodology and results have been divided into two sections: a) respiratory effects and b) circulatory effects.

a) *Respiratory Effects*

Method: This part of the study involved two groups of 6 patients each; and ventilation was measured using a spirometric technique with a modified Jaeger Spirotest III (7).

For premedication, atropine sulfate 0.6 mg was given one hour before anesthesia. Anesthesia was induced with sodium thiopental 500 mg, followed by halothane 2% in a high flow of oxygen to eliminate nitrogen from the lungs. When it was considered that a stable state of anesthesia had been achieved, the patient was transferred from the standard anesthetic machine to the spirometer circuit into which halothane was injected at a constant rate of 0.15–0.20 ml/min. This achieved a halothane concentration of 2 to 2.5% in the circuit throughout each experiment. The halothane concentration was measured with a Type 18 Joberg Interferometer which has an accuracy of 0.1%.

Following a period of control readings, pentazocine 30 mg or meperidine 30 mg was injected intravenously over 30 seconds. After 10 minutes the dose of

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the drug was repeated and observations were continued for a further 10 minutes.

From the spirometer tracing it was possible to determine minute volume, respiratory rate, tidal volume and oxygen consumption. Typical respiratory traces are shown in Figures 1 and 2. Serial samples of capillary blood were taken and $PaCO_2$ and pH determined using the Astrup apparatus. These samples were immediately placed on ice and the estimations made within 15 to 30 minutes.

Results: Individual results are shown in Figures 3 and 4 and the mean values are plotted in Figures 5 and 6. As can be seen, each drug produces a typical response, common to all patients in each group. To compare and contrast the respiratory effects, the mean results have also been plotted as percentage changes in Figure 5. The results have been statistically analyzed using students t/test and tested at the 2.5% level of significance.

Minute Volume: Both groups showed a statistically significant decrease after the first injection. In the pentazocine group, a minimum of 35% of the mean control value was reached in two minutes, a mean decrease of 4L min (Figs. 5 and 7). Subsequently the minute volume increased rapidly to 56% of the mean control readings, but was still significantly depressed ($p < 0.02$). The meperidine group reached a minimum of 59% of the mean control readings (a decrease of 3L min) three minutes after injection, thereafter slowly increasing

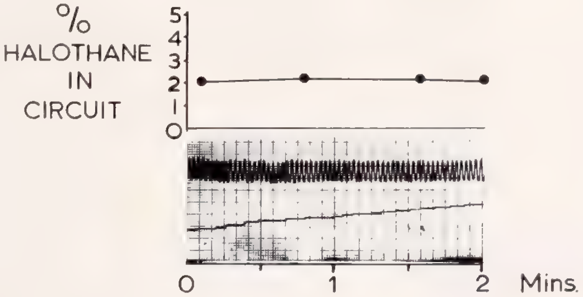

FIG. 1. Typical respiratory tracings during smooth anaesthesia. Lower line represents oxygen consumption.

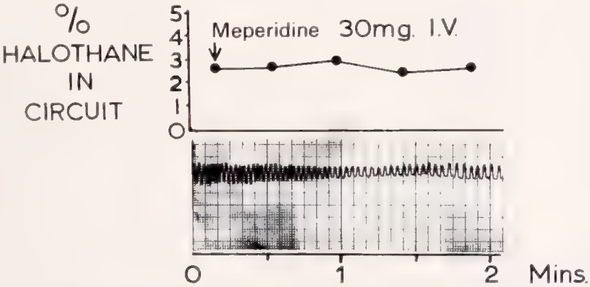

FIG. 2. Effect of meperidine on respiration during halothane anesthesia.

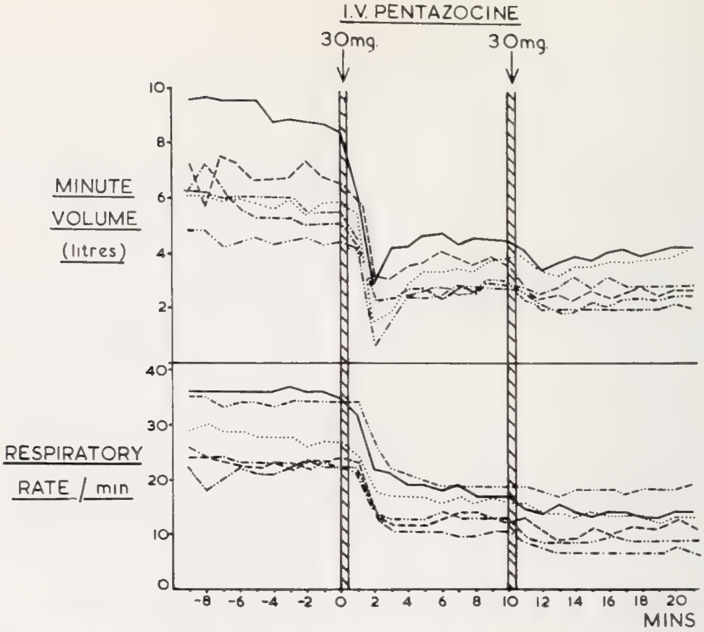

Fig. 3. Changes in minute volume and respiratory rate in 6 patients receiving IV pentazocine (2 × 30mg).

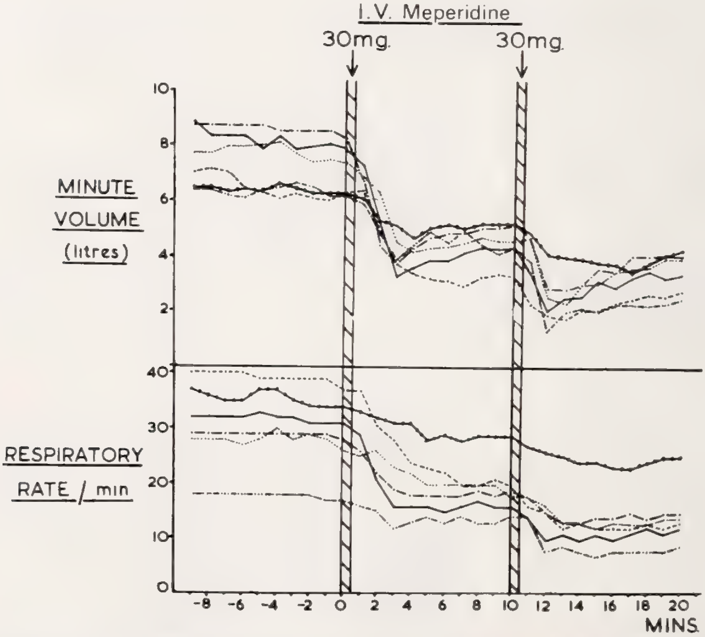

Fig. 4. Changes in minute volume and respiratory rate in 6 patients receiving IV meperidine (2 × 30mg).

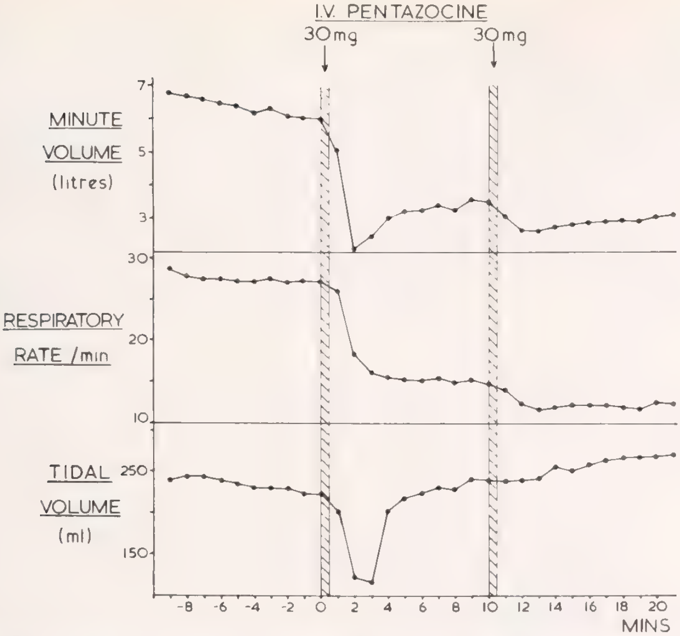

FIG. 5. Mean values for minute volume, respiratory rate and tidal volume in 6 patients receiving IV pentazocine (2 × 30mg).

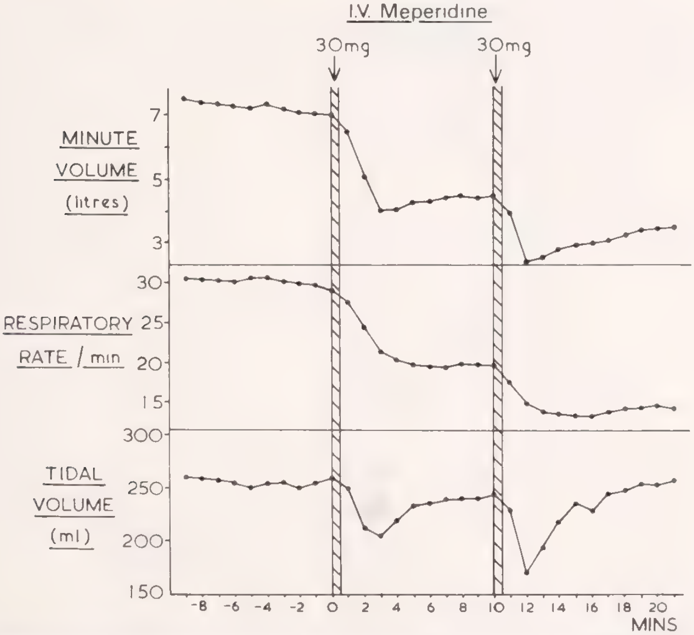

FIG. 6. Mean values for minute volume, respiratory rate and tidal volume in 6 patients receiving IV meperidine (2 × 30mg).

to 64%—both levels being significantly lower than control values ($p < 0.02$) (Figs. 6 and 7).

The response to the second injection of each drug differed markedly. Pentazocine caused a 20% decrease in minute volume (0.7L/min). This decrease was significant ($p < 0.02$) but thereafter minute volume increased to 92% of the mean of the three readings obtained prior to the second injection. Such depression was not significant. A second injection of meperidine, on the other hand, caused a depression of minute volume of the same degree as obtained with the first injection, namely, a maximum decrease to 54% of the pre-second-injection level, rising to 79% at 10 minutes—both levels being significantly reduced ($p < 0.02$).

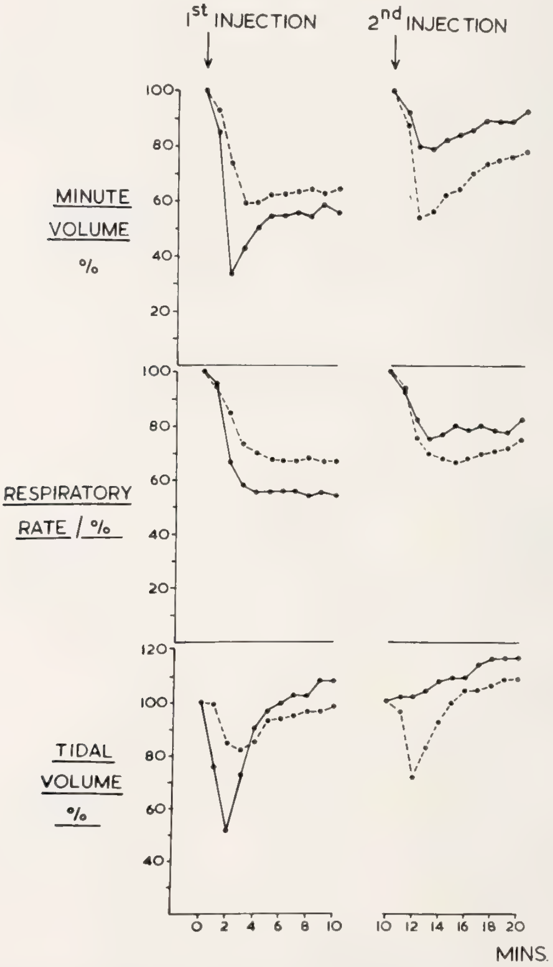

FIG. 7. Percentage changes in minute volume, respiratory rate and tidal volume after pentazocine (continuous line) and meperidine (interrupted line); 100% is taken as the value just prior to injection.

The difference in the responses between pentazocine and meperidine were significant ($p < 0.02$).

Respiratory Rate: Similar differences were seen in regard to respiratory rate. The first injection caused a slowing of the rate to 56% of the control readings with pentazocine and to 67% with meperidine (Figs. 5 and 6). Both reductions were significant ($p < 0.02$), but the difference between each drug was not significant. Following the second injection, pentazocine slowed respiration (to 80% of control) but to a much lesser extent than the first injection, whereas a second injection of meperidine slowed respiration to the same extent as after the first injection (i.e., to 68% of control).

Tidal Volume—Both drugs reduced tidal volume after the first injection (Figs. 5 & 6). The mean reduction was to 52% of the initial reading for meperidine and to 81% for pentazocine, being maximal after 2 minutes. Recovery was rapid and after 10 minutes both groups reached the pre-injection level. Following the second injection of pentazocine there was a slight increase in tidal volume whereas meperidine caused a decrease (to 71% of control) somewhat similar to that after the first injection. The difference between the two drugs after the second injection was significant ($p < 0.02$).

Blood Gases & Oxygen Consumption—Changes in $PaCO_2$ and pH were as expected following the degree of respiratory depression obtained (Figs. 8 & 9). Oxygen consumption was unaffected by either drug, the actual level being similar to that previously reported by Theye and Messick (1968) (8).

b) *Circulatory Effects*

Method: Thirteen patients were studied. As in the first part of the study, anesthesia was induced with sodium thiopental 500 mg one hour after pre-

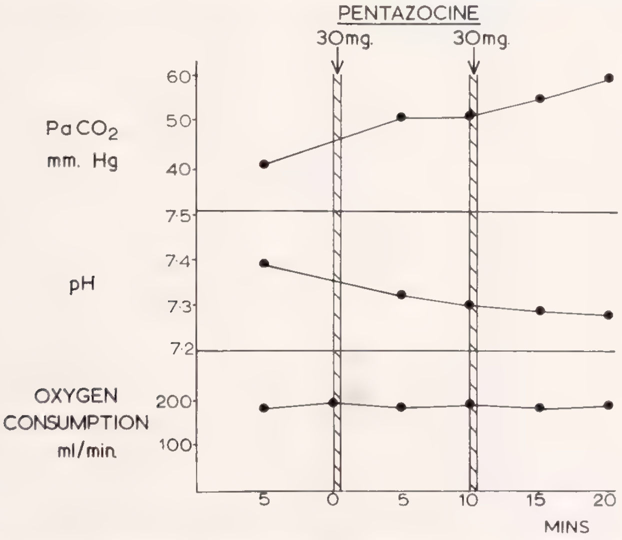

FIG. 8. Mean values of arterial carbon dioxide tension, pH and oxygen consumption in 6 patients before and after intravenous pentazocine (2 × 30mg).

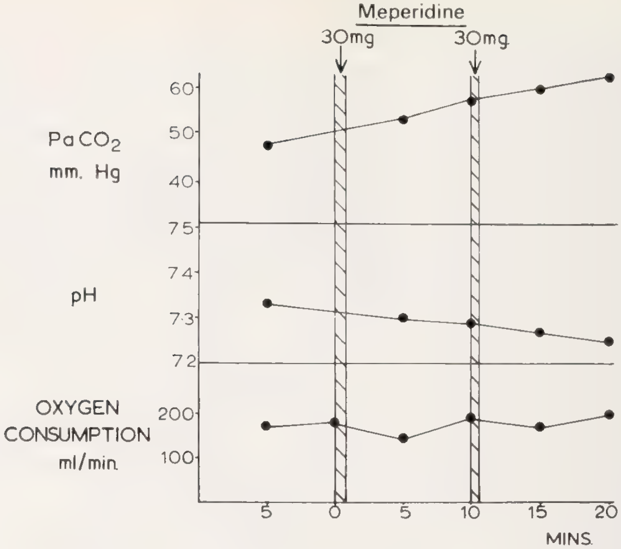

Fig. 9. Mean values of arterial carbon dioxide tension, pH and oxygen consumption in 6 patients before and after intravenous meperidine (2 × 30mg).

medication with 0.6 mg atropine sulphate. Anesthesia was maintained using nitrous oxide and oxygen (3:1L/min in a semi-closed system with carbon dioxide absorption) to which 1% halothane was added. A central venous catheter was inserted via an antecubital vein using the Seldinger technique.

Cardiac output was measured using the indocyanine green dye-dilution method with a Waters XE302 earpiece and densitometer. The difficulties of estimation using an earpiece are appreciated, especially in regard to calibration and presentation of the output in absolute terms, but when the ear is well vasodilated and posture is not altered, the method can show sequential changes in the same patient.

Electrocardiography was continuous and the heart rate was displayed by a Sanborn cardiotachometer 350–3400 A. Arterial pressure was measured by standard sphygmomanometry, the mean pressure being calculated as the diastolic pressure plus one-third of the pulse pressure. Central venous pressure was measured with a Sanborn 267 AC pressure transducer, the zero reference point being taken as 5 cm below the manubrium sterni. All electrical measurements were simultaneously recorded on a Sanborn 7700 6-channel recorder.

Following a period of control readings, injections of both drugs were given in an identical manner and timing as those previously described. Seven patients received two injections of 30 mg pentazocine and 6 patients received two injections of 30 mg meperidine.

Ventilation was spontaneous in all cases.

Results: The mean results are shown in Figures 10 and 11.

a) *cardiac output:* Following intravenous pentazocine, the cardiac output

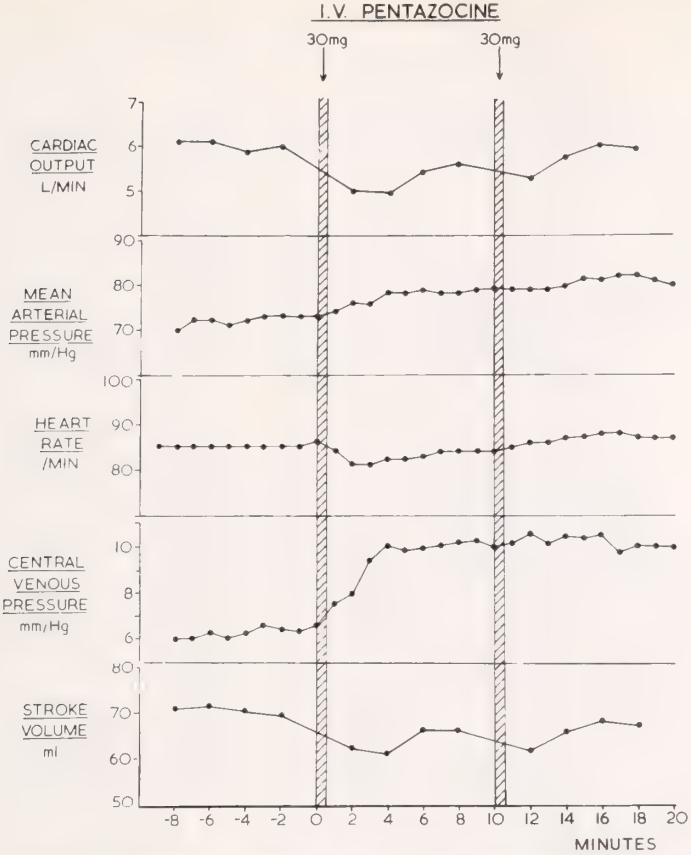

FIG. 10. Cardiovascular changes (mean of 7 patients) before and after IV pentazocine (2 × 30mg).

fell briefly by 20% recovering to almost control level after 10 minutes. A similar, but less marked, effect followed the second injection. The reduction after the first injection was statistically significant ($p < 0.01$), but that after the second injection was not significant. Meperidine produced almost the same pattern of change, the mean reduction being rather less.

b) *mean arterial pressure:* A small rise in mean arterial pressure occurred slowly in both groups of patients during the period of observation after the first injection.

c) *heart rate:* This did not change significantly after either drug; thus, cardiac output changes were in terms of stroke volume.

d) *central venous pressure:* Both pentazocine and meperidine caused a sharp rise in central venous pressure, this being more marked after pentazocine. The response of the CVP was rapid (Fig. 12) and the high pressure was maintained after recovery of the cardiac output to control levels. The rise in CVP was statistically significant ($p < 0.02$) in both groups of patients.

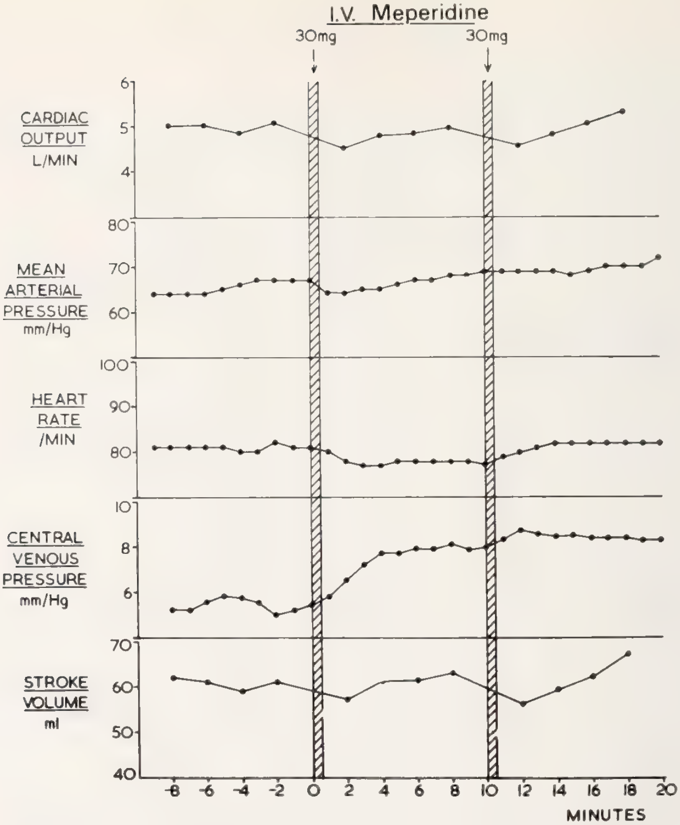

FIG. 11. Cardiovascular changes (mean of 6 patients) before and after IV meperidine (2 × 30mg).

Discussion

It would appear that, although both pentazocine and meperidine can cause significant respiratory depression during general anesthesia, they do have basic differences. While meperidine has a cumulative effect with repeated injection, pentazocine appears to lose much of its effect upon respiration. This confirms the observation of Hunter (9) from studies with animals.

It must be stressed that although identical doses of pentazocine and meperidine were used, they do not have equianalgesic potency. Pentazocine, when parenterally administered, is considered to have 2 to 2½ times the analgesic effect of meperidine (2, 10). It would therefore appear that pentazocine is a much safer drug in respect to respiratory depression than meperidine, especially when repeated injections are to be given, e.g., postoperatively or in obstetric practice.

The use of opiates as adjuvants to general anesthesia has found its main application in the technique of neuroleptanalgesia, and if spontaneous respiration is desirable, then pentazocine would appear to offer advantages. This has

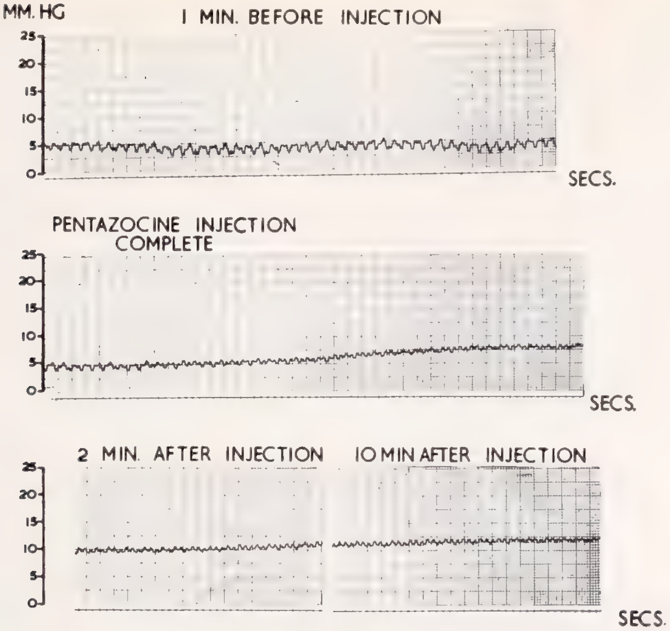

Fig. 12. Central venous pressure tracing in a patient receiving 30 mg pentazocine.

been the experience of Brown (11), who was able to use massive doses without producing undesirable degrees of respiratory depression.

Jennett, Barker, and Forrest (12), using pentazocine 20 mg intravenously in conscious volunteers, found a decrease of 20% in minute volume with little change in respiratory rate. In the present study, the fall in minute volume was over 60% of control value and was accompanied by a 40% decrease in respiratory rate. Obviously, the fact that a larger amount of drug was given must be considered, but it is reasonable to attribute much of the increased depression to the general anesthesia.

The most significant cardiovascular effects of these drugs were the fall in cardiac output and the marked and sustained rise in central venous pressure following the injection of both drugs.

The decreases in cardiac output were only small and transient and probably of little clinical significance. That the central venous pressure rose simultaneously with the fall in cardiac output would indicate a direct myocardial depressant effect, but one would expect the central venous pressure to fall after cardiac output returned to normal.

A complex situation however arises once respiratory depression occurs. Apart from the direct effects of the drug on the myocardium and the peripheral circulation, the rising carbon dioxide tension will have effects of its own tending to raise both cardiac output and arterial blood pressure (13, 14).

It is, therefore, difficult, on the data obtained, to explain in physiologic terms the sustained rise in central venous pressure. Rees et al (15) showed that neither meperidine nor di-acetyl-morphine (heroin) had any marked effect on central venous pressure when studying conscious patients suffering from coronary thrombosis. It is possible, therefore, that the effect is closely associated with the concurrent general anesthesia.

The factors which can affect central venous pressure are numerous. The sustained rise seen after administration of pentazocine and meperidine might be due to an augmentation of the venous return, resulting from an augmentation of the venous tone, or to a direct vasoconstrictor action on the pulmonary arterioles, although I have no evidence that this occurs. Jewitt, Maurer, and Tubner (16), using 30 mg or 60 mg pentazocine intravenously in conscious patients with myocardial infarction, found that there was an increase in pulmonary artery pressures and thought that this was due either to altered left ventricular function or to a direct increase in pulmonary vascular resistance.

The interpretation of central venous pressure during anesthesia is obviously far from simple and it would appear that it can be quite unrelated to flow.

Summary

Identical dosages of pentazocine and meperidine administered intravenously during general anesthesia caused a decrease in minute volume, respiratory rate, and tidal volume.

Significant differences between pentazocine and meperidine were shown only after a second injection following which meperidine caused further significant depression which pentazocine did not.

Cardiovascular effects included a fall in cardiac output, a small rise in mean arterial pressure, and no significant change in heart rate. Both drugs produced similar effects.

Both drugs caused a sharp rise in central venous pressure which persisted even after the cardiac output returned to control levels. The interpretation of this finding is discussed.

Acknowledgments

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Hypogammaglobulinemia and Malabsorption: Immunofluorescent Localization of Immunoglobulins in the Jejunal Mucosa

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The association of "acquired" hypogammaglobulinemia and malabsorption has been often described (1–11). Immunofluorescent investigation of the intestinal mucosa has been performed in only four cases, revealing few immunoglobulin-containing cells (1, 8, 9). In most instances, histologic examination showed changes similar to sprue. Recent observations of two patients with hypogammaglobulinemia and malabsorption with immunofluorescent localization of immunoglobulins are reported.

Case Reports

Case 1. A 64-year-old white woman was admitted to the hospital with pneumonia. She had a ten-year history of diarrhea, and seven years before she had been hospitalized with malabsorption and hypogammaglobulinemia. She also had recurrent bouts of pneumonia. She was treated with a gluten-free diet for four years with a reduction in stool frequency from eight to two times per day, but was on a regular diet for the past three years without deleterious effect. Two ml of gammaglobulin were administered intramuscularly weekly but her susceptibility to pulmonary infection did not improve. Physical examination revealed only rales bilaterally in the chest.

Laboratory data: Hemoglobin, 12.2 g/100 ml; white cell count, 8400/cu mm (69 neutrophils, 9 bands, 14 lymphocytes, 5 monocytes, and 3 eosinophils); serum folate, 8.2 ng/ml; serum vitamin B_{12}, 372 pg/ml; calcium, 9.4 mg/100 ml; phosphorus, 3.2 mg/100 ml; alkaline phosphatase, 230 units (normal 35–85); cholesterol, 167 mg/100 ml; serum vitamin A, 33 IU/100 ml (normal >80); serum carotene, 22 μg/100 ml (normal 40–100); serum electrophoresis: albumin, 3.8; alpha_1 globulin, 0.4; alpha_2 globulin, 1.1; beta globulin, 1.4; and gamma globulin, 0.1 g/100 ml. Chest x-ray showed a right upper lobe infiltrate and several atelectatic foci in the left lower lobe. Barium enema and upper gastrointestinal series with small bowel follow-through yielded normal results. Jejunal juice was examined and Giardia were not seen.

Special studies: Xylose and fecal fat were slightly abnormal and all serum immunoglobulins were low (Table I). Histologic examination of the jejunal mucosa revealed shortened and flattened villi with lengthened crypts, edematous lamina propria, and a paucity of plasma cells (Fig. 1). Lymphocytes and several eosinophils were seen scattered in the mucosa, and Peyer's patches were prominent. On immunofluorescent investigation, only a few plasma cells containing IgA were seen. Rare IgG and IgM containing plasma cells were detected. Complement (beta 1-c globulin) was not seen in the jejunal mucosa.

Case 2. A 51-year-old white woman was admitted with diarrhea of one year's duration. She had a complex history including a cholecystectomy many years earlier for cholecystitis, duodenal sphincterotomy one year later for pain which then subsided, a subtotal gastrectomy

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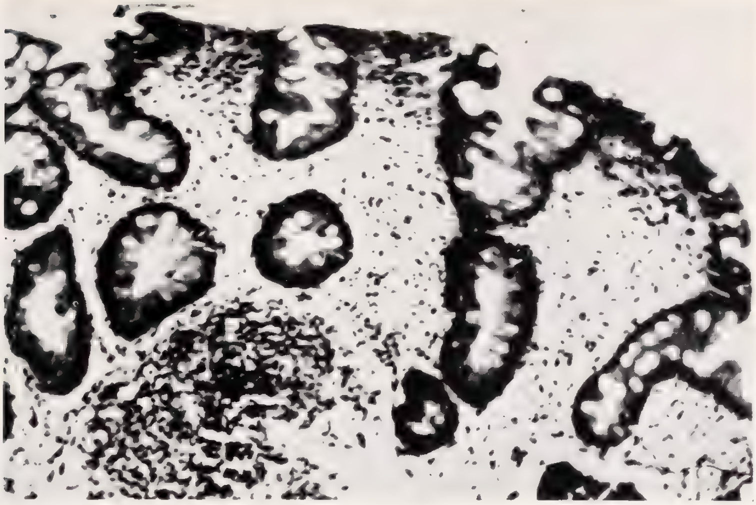

FIG. 1. Jejunal biopsy of patient 1. The villi are short and flattened (Hematoxylin and eosin stain × 100).

with a Billroth II procedure for bleeding duodenal ulcer two years before this admission, and excessive alcohol ingestion which ceased six years before. One year prior to admission, diarrhea developed with from 8 to 15 loose bowel movements a day. After hospitalization elsewhere, the patient was told that she had malabsorption and received monthly vitamin B_{12} injections, folic acid which she took for only a short time, and pancreatin which had no effect on the diarrhea and was stopped after a few months. Physical examination was unremarkable.

Laboratory data: Hemoglobin, 13.5 g/100 ml; white cell count, 9000/cu mm with a normal differential; serum folate, 5.6 ng/ml; serum vitamin B_{12}, 347 pg/ml; prothrombin time, 13/12; calcium 10.0 mg/100 ml; phosphorus, 3.9 mg/100 ml; alkaline phosphatase, 84 units; serum vitamin A, 127 IU/100 ml; serum carotene, 46 μg/100 ml; serum electrophoresis: albumin, 3.57; alpha$_1$ globulin, 0.42; alpha$_2$ globulin, 0.81; beta globulin, 1.30; and gamma globulin, 0.58 g/100 ml. Oral glucose tolerance test: fasting, 96; half-hour, 226; one hour, 232; two hours, 120; and three hours, 86 mg/100 ml (urines all negative); stool examination for ova and parasites was negative on two occasions. A secretin test was performed with the tube positioned in the efferent loop and a normal volume with a low bicarbonate, 58 mEq/L was collected. Rectal biopsy revealed normal mucosa.

Special studies: Xylose, fecal fat, and Schilling tests were all abnormal and serum immunoglobulins were all low (Table I). Histologic examination of the jejunal mucosa exhibited a normal villus pattern with rare clubbing of villi (Fig. 2). Plasma cells in the lamina propria were abundant (Fig. 3). Most of them contained IgG (Fig. 4). Fluorescein-labeled antiserum to IgA stained only rare plasma cells in the lamina propria (Fig. 5). Only rare IgM-containing cells could be seen. Complement was not detected.

Two biopsies obtained from patients with normal levels of immunoglobulin in the serum and with no abnormalities of the gastrointestinal tract revealed a normal villus pattern and, as previously described by Crabbe et al (12) a large number of IgA containing cells, and occasional IgM and IgG containing cells in the lamina propria (Table I).

Methods

Seventy-two hour fecal fat collection (13), 25 gram oral xylose absorption test (14), and 24-hour Schilling test with intrinsic factor (15) were per-

TABLE I

Absorption Data, Immunoglobulin Levels, and Immunoglobulin Distribution

	Normal values	Patient 1	Patient 2
Xylose	>4.5 g	3.8 g	3.5 g
24-hour fecal fat	<5.0 g	5.8 g	13.4 g
24-hour Schilling Test	>5.0%	—	2.0%
Serum (mg%)			
IgA	80–350	0	25
IgM	50–150	16	10
IgG	600–1400	40	250
*Jejunal Mucosa**			
Immunoglobulin-containing cells			
IgA	+++	±	±
IgM	+	±	±
IgG	±	±	++

* +++ = many; ++ = moderate; + = few; ± = rare.

formed. Quantitative serum immunoglobulin levels were determined by radial immunodiffusion technique (16). Jejunal biopsies were obtained with the Rubin hydraulic multiple biopsy tube (17). Biopsy specimens were frozen in dry-ice isopentane and stored at −60° C. Cryostat sections were stained with the following fluorescein-labeled antisera prepared as described previously (18): IgG, IgA, IgM, and complement (beta 1c globulin). Blocking with non-fluoresceinated antisera served as control for the specificity of the fluorescent staining.

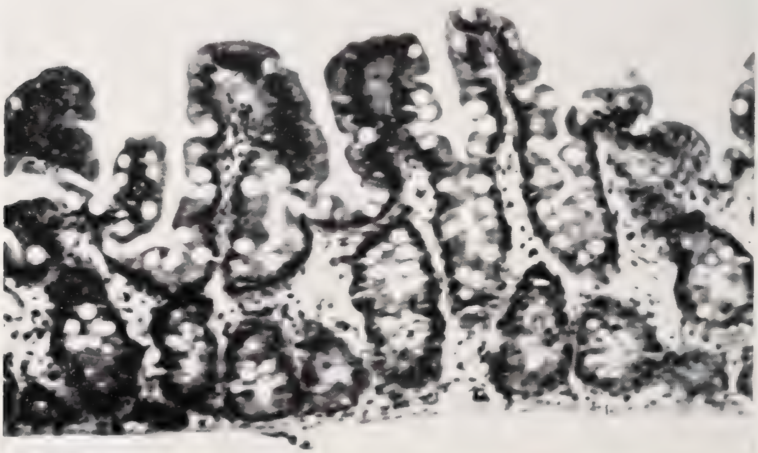

FIG. 2. Jejunal biopsy of patient 2. The mucosa has a normal villous pattern with slender elongated villi (Hematoxylin and eosin stain × 100).

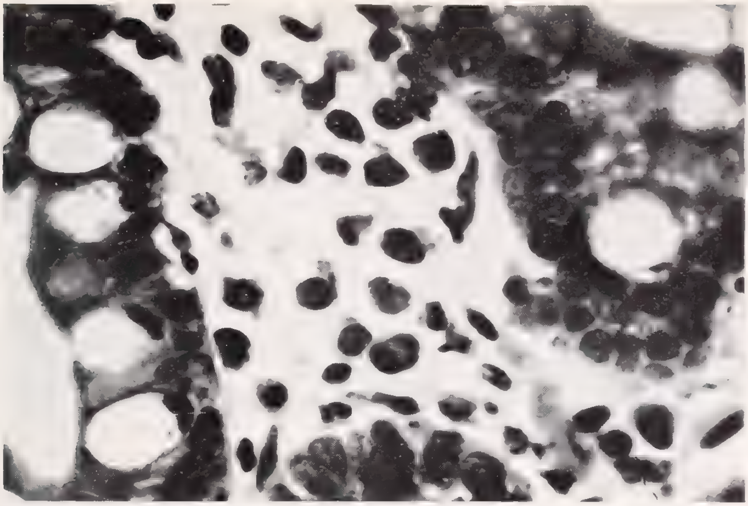

FIG. 3. Jejunal biopsy of patient 2. The lamina propria contains many typical plasma cells (Hematoxylin and eosin × 540).

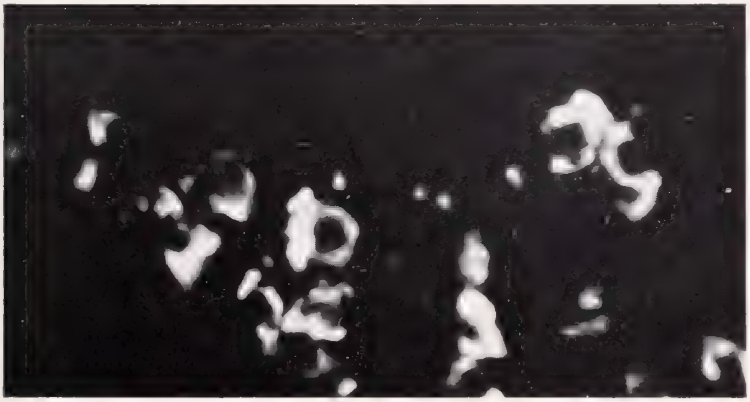

FIG. 4. Section of mucosa biopsy stained with fluorescein labeled anti human IgG antiserum. Several plasma cells contain IgG (× 54).

Discussion

Both patients had a reduction in all three major serum immunoglobulins and malabsorption. However, there were many differences between them. The first patient had a typical clinical course as described in "acquired" agammaglobulinemia (19) with recurrent pulmonary infections and markedly reduced to absent serum immunoglobulins. She had flattened sprue-like jejunal mucosa and a paucity of plasma cells. Immunofluorescence showed correspondingly rare immunoglobulin-containing cells in the lamina propria.

The jejunal mucosa of most reported cases (1–9) of hypogammaglobu-

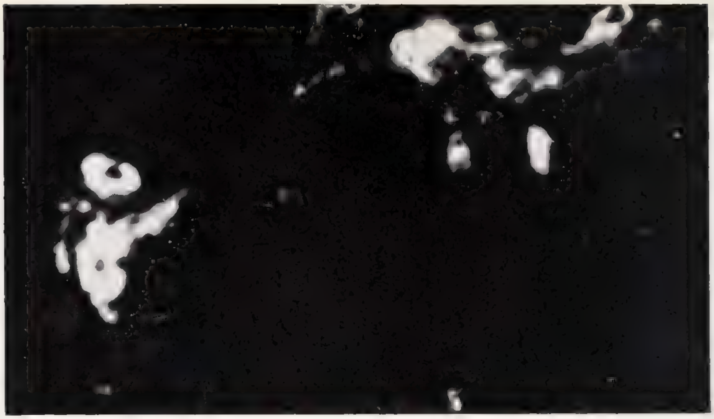

FIG. 5. A section parallel to that shown in Fig. 5 is stained with fluorescein-labeled anti-human IgA. Only rare plasma cells are stained (× 540).

linemia and malabsorption have been described as sprue-like with flattened villi, as in our first patient. Only two cases have been reported with normal villus architecture (10, 11). A decrease in plasma cells has been observed in all cases.

Few patients have been studied by immunofluorescence. Crabbe et al (1) reported one case of hypogammaglobulinemia with a jejunal mucosa showing flattened villi, decreased plasma cells, and decreased concentration of all immunoglobulins. Eidelman (8) reported two similar cases, and Gelzayd et al (9) another similar case. We are aware of no other reference to immunofluorescent studies of this entity, although this technique has been applied to isolated IgA deficiency (1) and to celiac syndrome (20, 21).

The second patient does not fit into the usual pattern. She did not have a history of recurrent sino-pulmonary infections. Her serum immunoglobulins were all low, but not as low as levels usually reported in this syndrome (19). Pancreatic insufficiency may have played a partial role in her malabsorption, though the secretin test is difficult to interpret after a Billroth II operation. However, in addition to steatorrhea, she had abnormal xylose and Schilling tests, and no clinical response to pancreatic enzyme supplementation. These factors provide strong evidence for a diagnosis of malabsorption at the intestinal mucosal level.

Histologic section of her jejunal mucosa appeared normal except for occasional blunted villi, and abundant plasma cells in the lamina propria, an observation not described in previous reports. However, immunofluorescent staining indicated a marked decrease in IgA- and IgM-containing plasma cells with IgG the main immunoglobulin present.

In normal jejunum, IgG is the least common immunoglobulin, IgA the most common with an IgA:IgM ratio of 6:1, and an IgA:IgG ratio of 10:1 (12). IgA has also been shown to dominate immunoglobulin secretion (22). In isolated IgA deficiency, plasma cells have not been decreased and they have contained mainly IgM (1). The observed predominance of IgG-containing cells in our patient can not be readily explained at this time, though it may merely reflect the predominance of IgG in her serum.

A patient has recently been described with hypogammaglobulinemia and Giardia whose jejunal mucosa reverted to normal after treatment (23). This observation, together with the finding of a normal mucosa in one of our patients, suggests that the mucosal abnormalities that have been previously described may be secondary to local insult rather than an initial factor. Our second patient may be in a relatively early phase of the disease.

The relationship between hypogammaglobulinemia and malabsorption is not yet understood. An abnormal small intestinal bacterial flora (24) has been reported in this entity and the association of Giardia lamblia with Type II dysgammaglobulinemia (25) also suggests increased susceptibility to intestinal infection, possibly due to local immunological deficiency. Both patients described support the concept that there is an association between decreased intestinal immunoglobulins and malabsorption.

Acknowledgment

We thank Dr. Eugene Ainbender for kindly performing the serum immunoglobulin determinations, and Dr. Henry Colcher for allowing us to study the first patient.

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Thyrotoxic Periodic Paralysis

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Introduction

Hyperthyroidism is frequently accompanied by muscle weakness and wasting to varying degrees. Most commonly the proximal and ocular muscles are more prominently affected. A less common type of muscle involvement in hyperthyroidism is periodic paralysis, generally of the hypokalemic variety. In the past three years we have evaluated five such cases at The Mount Sinai Hospital. This report describes our observations on this group of patients.

Case Reports

Case 1. A 24-year-old Filipino man was admitted to The Mount Sinai Hospital on December 5, 1969 complaining of two episodes of profound, diffuse muscle weakness during the preceding two-week period. Each episode was characterized by inability to support his weight when attempting to walk. There was no loss of consciousness, no confusion or dysarthria. Each episode cleared spontaneously over a period of two to four hours. Examination during each of these episodes showed the patient to be areflexic with diffuse muscle weakness. There was no atrophy.

Five years prior to admission he had been told that his thyroid was enlarged. Three months before admission he developed nervousness and tremulousness with an eight-pound weight loss despite good appetite. There was no family history of thyroid or muscle disorder.

Physical examination: The pulse was 120 per minute and regular. The skin was warm, soft, and smooth. The thyroid gland was estimated to be approximately 45 Gm and had a "cobblestone" texture. There was a fine tremor of the hands and tongue. There was no apparent muscle weakness.

Laboratory data: Serum PBI was 11.6 mcg/100 ml. Serum potassium levels on two occasions were 3.4 mEq/L and 4.1 mEq/L respectively. Intravenous infusion of glucose and insulin resulted in a recurrence of the profound weakness. Simultaneous serum potassium was 2.8 mEq/L. Electromyography during the period of induced weakness showed "no motor units" on attempted active efforts. The 24-hour radioactive iodine uptake was 64%.

On December 12, 1969 treatment was started with potassium chloride. On December 17, 1969 the patient was treated with 4.0 millicuries of ^{131}I. He subsequently became euthyroid and has experienced no further episodes of muscle weakness.

Case 2. A 25-year-old Filipino man was admitted to The Mount Sinai Hospital on August 25, 1969 with complaints of weakness, nervousness, and a 35-pound weight loss of three months' duration. His appetite was good. Two months prior to admission he developed diarrhea, increased sweating, hair loss, burning of both eyes, and palpitations. One month prior to admission he was aware of weakness and muscle pains in both legs which caused him to fall on several occasions. There was no family history of thyroid or muscle disease.

Physical examination: The pulse was 108 per minute and regular. There was mild chemosis and slight lid lag. The thyroid gland was estimated to be approximately 60 Gm and was moderately firm, non-tender, smooth, and contained no nodules. A bruit was present. There was fine tremor of the fingers of both hands. There was no muscle weakness.

Laboratory data: Serum potassium on two occasions was 2.8 and 3.4 mEq/L. Serum

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PBI was 17.0 mcg/100 ml. The 24-hour radioactive iodine uptake was 65%. The T_3 uptake ratio was 2.12 (normal 0.8–1.3).

Treatment was instituted with Tapazole®, phenobarbital, and saturated solution of potassium iodide. On October 2, 1969 Tapazole® was discontinued because of rash and pruritus. On October 7, 1969 6.2 millicuries of ^{131}I was given. This treatment failed to control the hyperthyroidism, and periodic episodes of weakness continued to occur. On October 9, 1969 the 24-hour radioactive iodine uptake was 59%, and an additional 3 millicuries of ^{131}I was administered.

By January 1970 the patient was euthyroid. He has experienced no further episodes of weakness.

Case 3. A 33-year-old Chinese man was admitted to The Mount Sinai Hospital for the first time on June 5, 1970 for increasing frequency of episodic and self-limiting weakness of two months' duration. For two weeks prior to admission the episodes occurred almost daily, primarily in the lower extremities and, to a lesser extent, in the upper extremities. The weakness was proximal in distribution. On the morning of admission the weakness was sufficiently profound that he was unable to get up from bed and had difficulty in using his upper extremities. There was no history of sensory, sphincter, or respiratory involvement.

For the ten years prior to admission he had been thin, unable to gain weight, and complained of heat intolerance. There was a slight tremor of both upper extremities which was attributed to nervousness. Prior to admission he was found to have a PBI of 13 mcg/100 ml. The 24-hour radioactive iodine uptake was 62%. He was treated with 2.4 millicuries of ^{131}I on the day prior to admission.

One brother had thyrotoxicosis.

Physical examination: The pulse was 104 per minute. The thyroid was minimally enlarged, smooth, nontender, and without bruits. No nodules were palpable. There was mild proximal muscle weakness and slight tremor of both outstretched hands.

Laboratory data: Four serum potassium levels ranged from 4.9 to 4.7 mEq/L. On one occasion, when the patient was noted to be limping, the serum potassium was 3.9 mEq/L. Creatine phosphokinase levels were 4.2, 5.4, and 7.2 units (normal less than 4.5 units).

Glucose and insulin infusion and muscle biopsy were refused. Treatment with Lugol's solution was initiated and the patient was discharged. The patient became euthyroid and has experienced no further episodes of weakness.

[Though significant hypokalemia was not documented, the history is sufficiently typical of thyrotoxic periodic paralysis to be included in this series.]

Case 4. A 43-year-old Caucasian man was admitted to The Mount Sinai Hospital for the first time on September 8, 1970 because of recurrent episodes of muscle weakness. The symptoms first appeared six months prior to admission. Four months prior to admission he had two episodes, during which he fell to the floor without loss of consciousness. The episodes usually developed after eating heavily. Muscle biopsy and electromyography done at another hospital were said to have been normal. A glucose tolerance test was reported to have provoked weakness. Serum potassium drawn during an episode of profound weakness was 2.7 mEq/L.

A 67-year-old uncle of the patient has had episodes of muscle weakness over the past 25 years and has been told of a low serum potassium.

Physical examination: The pulse was 100 per minute and regular. The skin was warm, soft, and moist. The thyroid gland was estimated to weigh approximately 40 Gm, was rubbery, and contained no distinct nodules. There was a fine tremor of both hands. No muscle weakness was demonstrable.

Laboratory data: PBI was 13.4 mcg/100 ml. The 24-hour radioactive iodine uptake was 95%. The resting serum potassium level was 4.5 mEq/L. On glucose and insulin infusion the serum potassium fell to 2.5 mEq/L. There was simultaneous muscle weakness, most marked in the lower extremities.

On September 30, 1970 the patient was treated with 3.0 millicuries of ^{131}I. He was noted to be euthyroid on December 2, 1970, and has experienced no further episodes of weakness since becoming euthyroid.

Case 5. A 27-year-old Filipino man was first evaluated in April 1967 following three episodes of relatively sudden and profound muscle weakness during the preceding six-month period. With each episode he became profoundly weak and was unable to get out of bed or to stand unaided. The episodes usually occurred in the morning, but could not be specifically traced to any unusual exertion over the prior 24-hour period. The episodes were self-limited and cleared over the ensuing one to four hours. No sensory symptoms were present. Examination performed toward the end of one such episode showed him to be areflexic with diffuse weakness accentuated in the proximal musculature. The cranial muscles were not involved.

He had been aware of easy fatigability, palpitations, and irritability over the previous year, but had never sought medical advice. His weight had been relatively stable but there was tremulousness which had not previously been noted. He was unaware of any family history of thyroid or muscle disease.

Physical examination: The pulse rate was 110 per minute and regular. The skin was warm, smooth, and moist. The thyroid gland was symmetrically enlarged to approximately 35 Gm and contained no nodules. No bruits were heard. A fine tremor was present in both outstretched arms and muscle weakness was present in the shoulder and hip girdles. Deep tendon reflexes were present and equal. There were no Babinski signs or sensory changes.

Laboratory data: PBI was 12.8 mcg/100 ml. The 24-hour radioactive iodine uptake was 70%. Serum potassium at the time of examination was 3.9 mEq/L. Serum potassium drawn during the third episode of muscle weakness was 2.9 mEq/L. Electromyography performed during a normal period showed a diffuse increase in short duration polyphasic potentials. Conduction times were normal.

In May 1967 he was treated with 4.0 millicuries of ^{131}I. He subsequently became euthyroid and has had no further episodes of weakness.

Discussion

Approximately 250 cases of thyrotoxic periodic paralysis have been reported in the world literature. Most of these cases have occurred in Oriental patients. Among Oriental patients with thyrotoxicosis, the incidence of periodic paralysis is approximately 2% (1, 2). Though hyperthyroidism occurs seven times more frequently in females than it does in males (3), approximately 90% of the reported cases of thyrotoxic periodic paralysis occurred in males. Between 8.2% (2) and 13% (1) of Oriental males with thyrotoxicosis develop periodic paralysis, while between 0.17% (1) and 0.4% (2) of Oriental females with thyrotoxicosis have periodic paralysis. The incidence of periodic paralysis among Caucasians and Negroes with thyrotoxicosis is not known. The peak age range for development of periodic paralysis in thyrotoxicosis is 20 to 39 years of age (2), while the peak age range for development of nonthyrotoxic periodic paralysis is during adolescence (4). The onset of periodic paralysis usually coincides with or follows the onset of hyperthyroidism, but the periodic paralysis may also precede the thyroid abnormality (2). Less than 1% of the reported cases of thyrotoxic periodic paralysis in Orientals had a familial incidence of periodic paralysis (2).

Return of thyroid function to the euthyroid state almost always results in complete cessation of the periodic paralysis.

Table I summarizes the clinical features of the present series. All of our patients were males, and four of five were Oriental. Interestingly, the only patient in this group with a family history suggestive of periodic paralysis was Caucasian. The age range in our group was 24 to 43 years. All of our patients experienced no further episodes of paralysis following successful control of the

TABLE I

Case No.	Sex	Age	Race	Familial muscle weakness	Serum K+ during episode	EMG findings	Frequency of episodes of weakness	RAI uptake	Treatment	Response to therapy
1	Male	24	Oriental	0	2.8 mEq/L	"myopathic"	weekly	65%	^{131}I	No weakness following euthyroid state
2	Male	25	Oriental	0	2.8 mEq/L	not done	infrequent	65%	^{131}I	No weakness following euthyroid state
3	Male	33	Oriental	0	3.9 mEq/L	"myopathic"	daily	62%	^{131}I	No weakness following euthyroid state
4	Male	43	Caucasian	1	2.7 mEq/L	normal	biweekly	98%	^{131}I	No weakness following euthyroid state
5	Male	27	Oriental	0	2.9 mEq/L	short duration polyphasic potentials	monthly	70%	^{131}I	No weakness following euthyroid state

hyperthyroidism. In all but one of our patients, a low serum potassium was demonstrable during spontaneous or induced paralysis.

The paralytic episodes of thyrotoxic periodic paralysis are essentially the same as those in idiopathic hypokalemic periodic paralysis. The serum potassium is usually low and the attacks can be precipitated by carbohydrate loading. The skeletal muscles are flaccid and areflexic, and are unresponsive to electrical stimulation. Treatment with potassium replacement frequently restores muscle function to normal, thereby terminating an attack.

It has been thought that patients with this syndrome have a constitutional latent metabolic defect which makes their musculature more sensitive to hypokalemia in the presence of excessive thyroid hormone. This theory is supported by the observation of Okihiro and Nordyke that large doses of thyroid hormone given to a euthyroid patient who had had thyrotoxic periodic paralysis in the past resulted in a recurrence of the periodic paralysis (5). Patients with idiopathic hypokalemic periodic paralysis do not experience more frequent attacks when iatrogenically made hyperthyroid.

Resnick et al have shown that the hyperactivity of the sympathetic nervous system is not an essential feature of the mechanism by which hyperthyroidism predisposes certain patients to hypokalemic periodic paralysis (7). What role, if any, aldosterone plays in the development of thyrotoxic periodic paralysis has not been clarified. There is some evidence to suggest that during attacks of paralysis, urinary aldosterone levels may be increased.

Acknowledgment

We are most grateful to Dr. Samuel Waxman for referring Case 3 and to Dr. Kermit Osserman for referring Case 4 to us.

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Papillary Cystadenoma of the Kidney Report of a Case Exhibiting Clinical Symptomatology and a Review of the Literature

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Adenomas of the kidney producing symptoms and signs are rare, only fifty such cases having been reported (1). Of the various histologic types, the papillary form is most common and is usually associated with either gross or microscopic cysts (2). Those cases with gross cystic features must be distinguished from multilocular renal cysts, which are unilateral.

A large cystic papillary adenoma which produced a clinically palpable mass is reported here, with a review of the differential features of cystic renal lesions.

Case Report

A 79-year-old white woman was admitted to the Hospital for Joint Diseases and Medical Center on June 3, 1970 with a complaint of progressively enlarging mass on the left side of the abdomen for three years. She was chronically constipated and had occasional dizzy spells and headache. There were no symptoms of urinary tract disease. There was no significant individual or family history.

On examination, the pulse was 82 per minute, temperature 98° F, and blood pressure 160/95 mm of Hg. There was a large mass extending from the left lumbar area to the pelvic region, which was slightly mobile. The mass was firm in consistency and mildly tender. It was not fixed to the abdominal wall. On rectal and vaginal examination, the lower margin of the mass was felt in the left side of the pelvis.

Laboratory data included a hemoglobin of 12.8 grams percent, hematocrit 41 percent, and WBC 4.400, with a normal differential. Urine specific gravity was 1.010, pH was 7.0; there was no albumin or sugar; WBC and RBC, 1 to 2 per high power field, blood urea nitrogen, 22 mg. percent, fasting blood sugar, 102 mg percent. Urine culture showed Pseudomonas aeruginosa, and the colony count was over 100,000 per ml. A flat plate of the abdomen showed a homogeneous density in the left side of the abdomen, continuous with the kidney shadow, and obliteration of the psoas margin. A contrast study of the colon revealed displacement of the sigmoid and the descending colon to the opposite side, with extrinsic compression of the bowel wall. Contrast study of the kidneys and ureters showed a large left lower pole mass with spreading of the calyces, but no distortion (Fig. 1). No increased radiolucency or calcification was noted within the mass.

An exploratory operation was performed on June 6, and a large retroperitoneal mass measuring 16 x 6 cm, was found in the left side of the abdomen replacing the lower pole of the kidney. The mass was excised by means of a partial nephrectomy.

Gross examination of the mass revealed a lobulated, multicystic structure, weighing 600 grams and measuring 16 x 6 x 4 cm (Fig. 2). The outer surface was covered with a capsule which was focally separable. The cysts varied from 0.4 to 4 cm and they contained clear to hemorrhagic fluid. The cut surface showed a multicystic spongy appearance, with areas of thick, whitish, fibrous tissue and focal areas of yellowish, homogeneous appearance. No normal kidney tissue was seen grossly.

Microscopically, the tumor had both cystic and solid areas. The cysts are lined by simple

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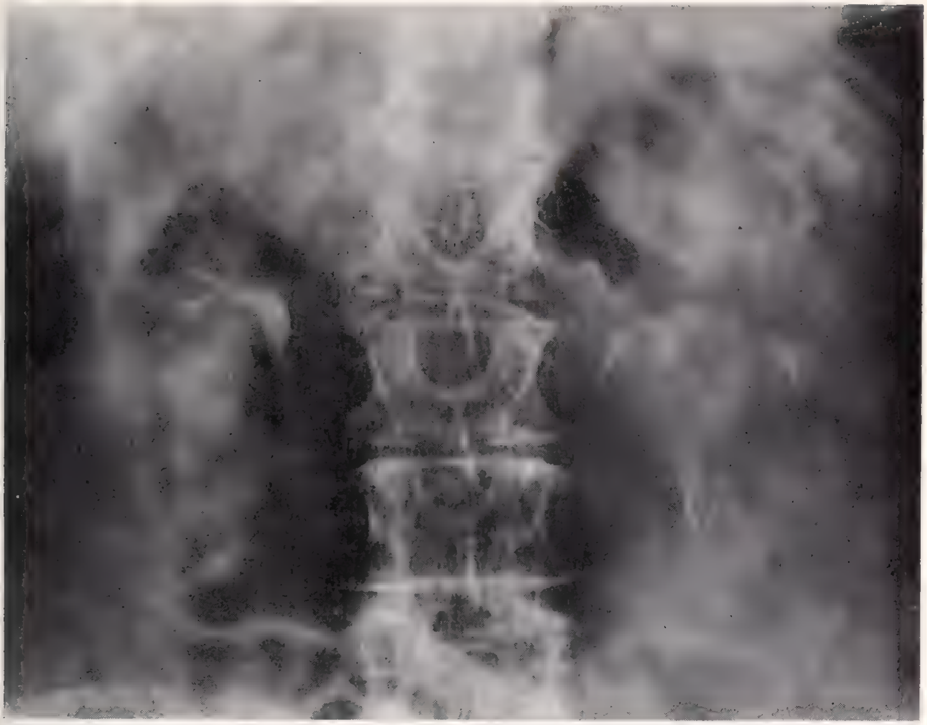

Fig. 1. Intravenous pyelogram showing large left lower pole mass with spreading of calyces, but no distortion of their contours. There is no calcification within this mass.

cuboidal epithelium and were separated by thin connective tissue septa, which were devoid of renal tubules or glomeruli (Fig. 3). The more solid areas showed an adenomatous pattern with proliferating glands lined by high cuboidal to tall columnar epithelium arranged in papillary fashion (Fig. 4). The cell cytoplasm was strikingly eosinophilic and contained coarse hemosiderin pigment, giving the appearance of "apocrine" type of epithelium (Fig. 5).

The postoperative period was uneventful and the patient has been free of symptoms for a period of one year.

Discussion

In 1950, Abeshouse described sixteen different varieties of renal cyst (3). Spence (4), in 1955, for the first time, drew a line of distinction between polycystic disease, multicystic disease, and multilocular cysts. True polycystic disease of the kidney is almost invariably bilateral and ultimately fatal; whereas, multicystic disease and multilocular cysts are usually unilateral and the prognosis is not so poor. All of these lesions are more common in the younger age groups, but they can occur in adults; multilocular cysts usually occur in the adult age group. Histologically, polycystic kidney can be differentiated from multilocular cysts of the kidney on the basis of the presence of residual normal parenchyma interspersed between the cysts in polycystic kidney. The multilocu-

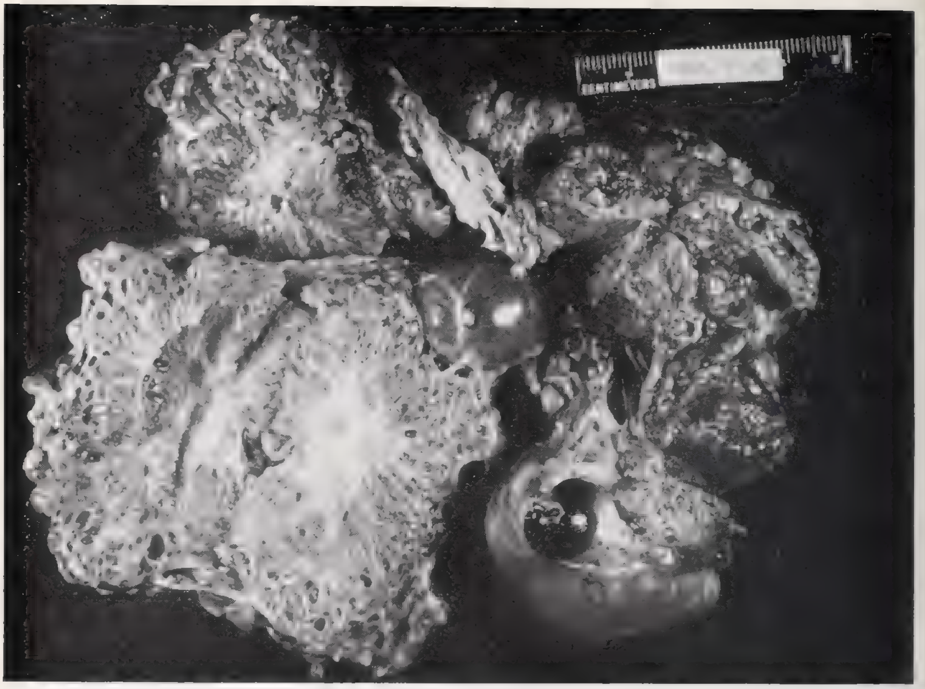

FIG. 2. Cut surface of large lobulated multicystic tumor removed from lower pole of left kidney. The tumor is spongy and the cystic spaces vary from pin-head size to 4.0 cm. in diameter.

lar cysts are sharply demarcated from adjacent renal tissue and do not contain any mature functioning nephrogenic tissue within their septa. There is hardly any histologic difference between multilocular cysts and multicystic disease of the kidney. The latter condition involves the entire kidney, whereas only a portion of the kidney becomes involved in a multilocular renal cyst (5). The differential features of cystic lesions of the kidney are shown in Table I.

Cystadenomas of the kidney and multilocular renal cysts are two different entities which may be difficult to differentiate on gross morphologic grounds. Both conditions are usually unilateral and can occur at any age. Morphologically, both contain epithelial-lined cysts, and they are demarcated from the uninvolved kidney by thick bands of connective tissue (5). Microscopically, however, the cystadenomas usually show a tall columnar epithelium with papillary infoldings lining, and sometimes filling, the cyst cavities (5). This feature was observed in the present case.

Multilocular renal cyst is a rare condition and very little is known about its etiology and pathogenesis. There are several reported cases in the literature (6, 7, 8, 9, 10). The coexistence of Wilm's tumor and of clear cell carcinoma with multilocular cysts has been observed by some investigators. (10, 11) Some have noticed embryonic, nonmalignant structures in the stroma of the dividing septa (4, 5). These findings led Uson and Melicow (10) to raise the question as to whether this condition is a cystic malformation or a true neoplasm.

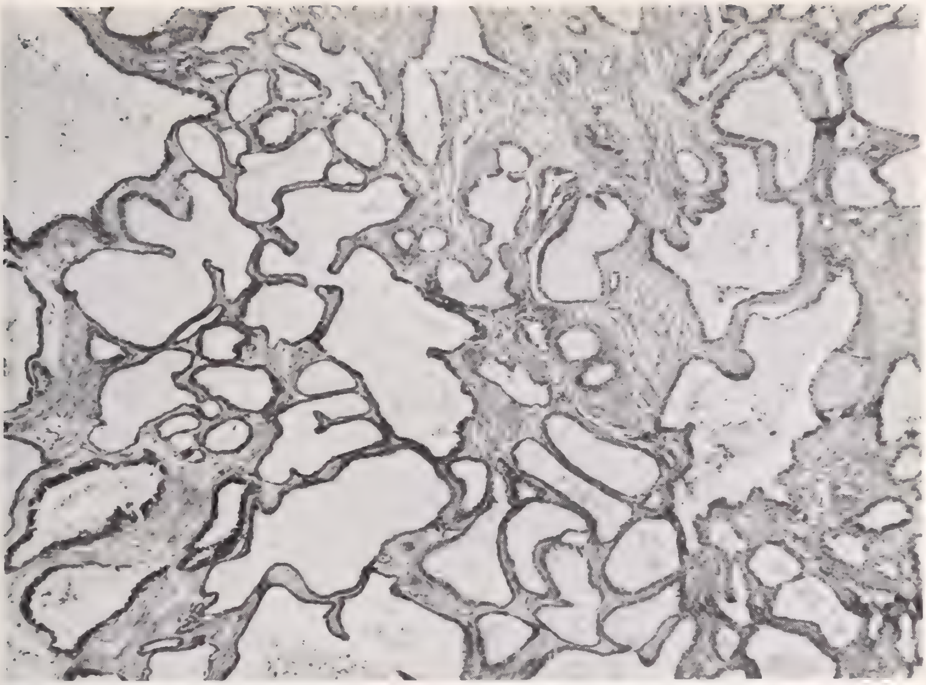

FIG. 3. Photomicrograph of cystic area of renal tumor showing fibrous septa and simple cuboidal epithelial linings in cystic spaces. (H.E., x 100)

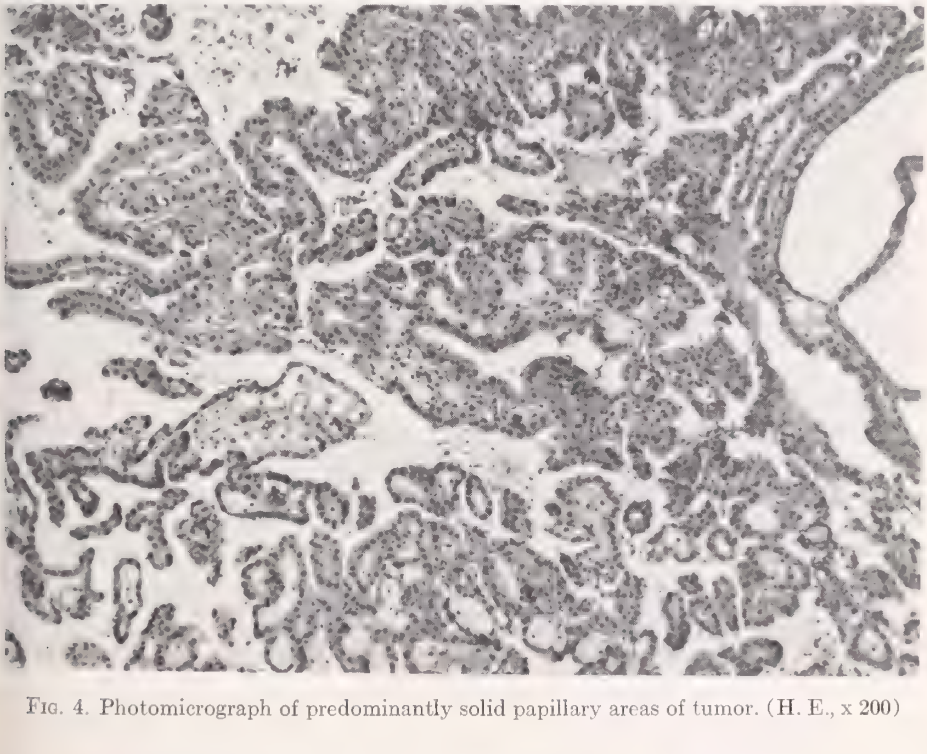

FIG. 4. Photomicrograph of predominantly solid papillary areas of tumor. (H. E., x 200)

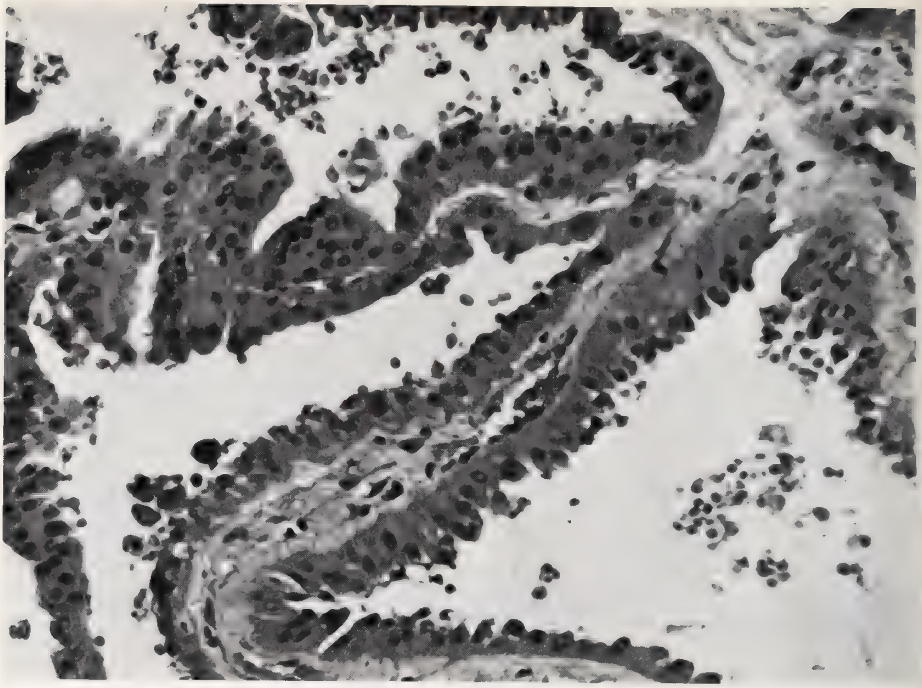

Fig. 5. "Apocrine" type of columnar epithelial lining cells containing hemosiderin pigment were seen in focal areas of the cystic tumor. (H. E., x 320)

Adenomas of the kidneys without clinical signs or symptoms are quite common (2). The rare symptomatic renal adenomas were reviewed by Cristol, Bothe, and Grotzinger (1). They studied forty-nine reported cases and one additional case of their own. Their study showed that this tumor can occur at any age without any sex predilection, though the overall incidence of renal adenomas is more common in males. They vary from pinhead size to large masses. The largest, weighing 22 pounds, was reported by Gordon-Taylor (12). About 80 percent of the cases studied presented with a palpable mass in the abdomen. More than 60 percent complained of pain in the renal area and some had gross hematuria (1). The present case had no complaint other than abdominal swelling. The adenomas can be either cystic or solid. Of the cystic varieties, papillary cystadenoma is most common (2).

The malignant potential of these tumors is controversial. Bell (13) suggested that the tumors measuring less than 3 cm in diameter do not metastasize. Some investigators disagree with this contention. (1, 14, 15). Allen (2) thinks tumors less than 5 to 6 cm in diameter rarely produce metastases. Often, it is extremely difficult to be certain on purely histologic grounds, whether a tumor is malignant, even when it is large. Unfortunately, the reported cases of symptomatic renal adenomas do not include sufficient follow-up information to establish their long term behavior. Our case, while larger than 6 cm, has shown no clinical evidence of malignancy during the short follow-up period.

TABLE I

Differential Diagnosis of Cystic Lesions of Kidney

Disease	Incidence	Heredity	Age	Laterality	Gross features	Microscopic features	Nature of lesion	Prognosis
Polycystic disease, adult	Rare, more common than infantile.	Dominant	Usually adult	Bilateral	Large kidney with multiple cysts involving both cortex and medulla	Cysts are lined by variable epithelium and interspersed with normal parenchyma	Cystic malformation	Poor
Polycystic disease, infantile	Rare	Recessive	Infancy	Bilateral	More or less same picture as adult type	Nondescript lining of the cysts with foci of normal nephrons	Cystic malformation	Very poor
Multicystic disease	Very rare	None	Usually infancy; may occur at any age	Unilateral	Entire kidney is involved by multiple cysts of varying sizes.	Cysts are lined by a single layer of flattened epithelium. The intervening septa are composed of thick bands of connective tissue with infantile tubules and glomeruli, interpreted as embryonal remnants.	Cystic malformation	Good
Multilocular cyst	Very rare	None	Any age	Unilateral	Well circumscribed multilocular cyst with thick capsule, involving a portion of the kidney.	Cysts are lined by flattened epithelium. No functioning renal parenchymal tissue is seen between the cysts.	Cystic malformation	Good
Cystadenoma	Very rare	None	Any age	Unilateral	Well circumscribed partly solid and partly cystic mass or multilocular cyst with a thin capsule, involving a portion of the kidney	Cysts are lined by high cuboidal or columnar epithelium, sometimes showing papillary infoldings. No parenchymal tissue is seen between the cysts.	Neoplasm	Good

Summary

A case of papillary cystadenoma of the kidney is reported which, by its large size, produced clinical symptoms. A review of other examples of this rare neoplasm is presented, with a discussion of the differential diagnostic features of cystic renal lesions.

Acknowledgment

The authors wish to express their gratitude to Daniel Casten, M.D. for permission to report this case, and to Fabius Fox, M.D., for review of the roentgenograms.

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Subepithelial Hemorrhage of Renal Pelvis Simulating Neoplasm (Antopol-Goldman Lesion)

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In 1948, Antopol and Goldman were first to describe subepithelial hemorrhage of the renal pelvis simulating neoplasm and reported seven cases of thi entity. During the past two decades, despite significant advances in renal pyelographic and arteriographic techniques, no further cases have been reported.

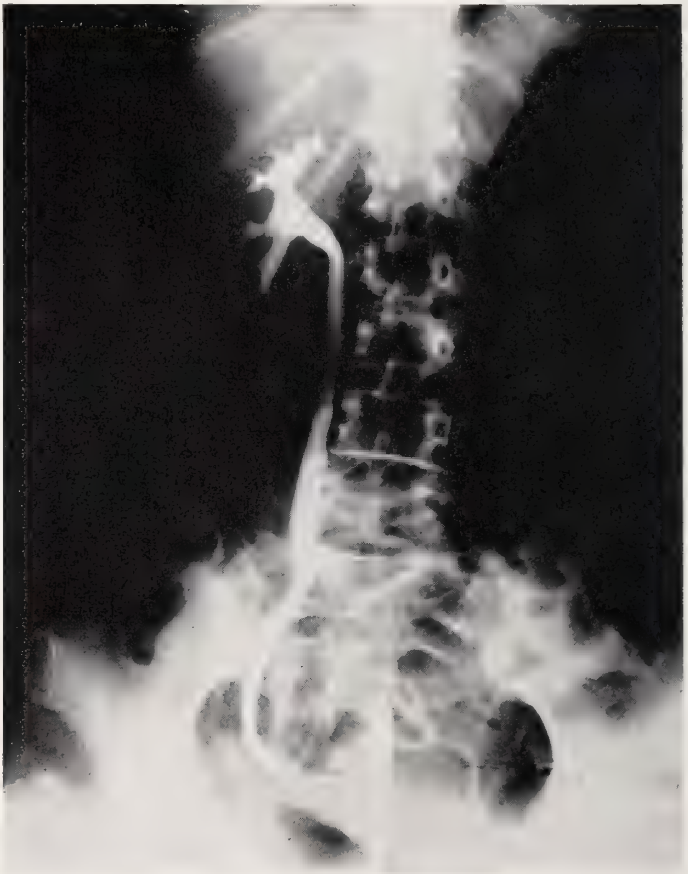

Fig. 1. Retrograde pyelogram showing good visualization of the pelvis and calyces.

Clinically, the two constant findings which lead to a diagnosis of neoplasm ar gross or microscopic hematuria and filling defects in the renal pelvis on roentge studies. Antopol and Goldman stressed the importance of a history of trauma

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even though slight, or sudden change in motion. Lack of awareness of the existence of this lesion does not permit consideration in the differential diagnosis and inevitably leads to complete surgical removal of the kidney involved. Total nephrectomies were performed on all previously reported cases as well as two of the three cases reported below. Case 3 underwent partial nephrectomy with excellent results.

Case Reports

Case 1: A 42-year-old housewife came to the Emergency Room because of gross hematuria and severe right flank pains of four days' duration. The pains were sharp and severe during the day and radiated anteriorly. Laboratory findings on admission were within normal limits except for gross bloody urine. The blood count was normal, with 10.4 grams hemoglobin. An excretory urogram showed a large right kidney with several opacities on the preliminary film. Following the injection of contrast medium, a five-minute film revealed marked intensification of the right renal cortex without visualization of the pelvic or calyces. On subsequent films there was progressive intensification of the cortex of the right kidney; at 2 hours and 8 hours, the outline of the pelvis and calyces were distinct (Fig. 1). The impression at this time was a probable blockage of the right outflow tract close to the pelvis without a demonstrable calculus. Cystoscopy and a retrograde pyelogram four days after admission showed excellent visualization of the right ureter, pelvis, and calyces (Fig. 1). A repeat retrograde pyelographic examination four days later demonstrated partial visualization of the right pelvis and calyces. In addition, there was intensification of the cortex and poor visualization and delineation of the calyces on subsequent films. A right retrograde pyelogram on the following day revealed a collection of contrast medium between the middle and lower calyces which appeared to press on the renal pelvis. On March 25, 1969 a right nephrectomy was performed.

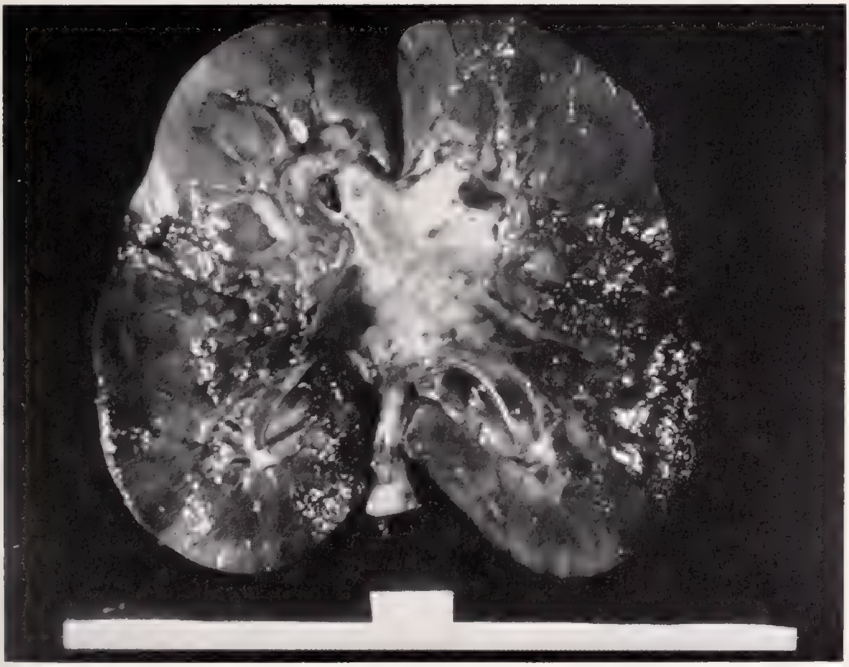

Fig. 2. Submucosal hemorrhages in the pelvis and middle and lower calyces (× 100).

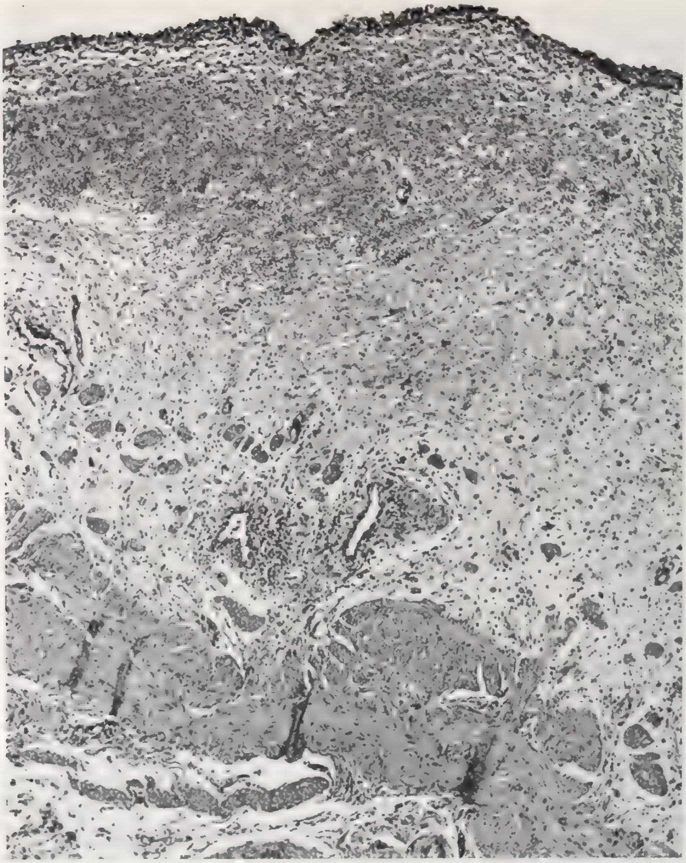

FIG. 3. Subepithelial pelvic hemorrhage with elevation of overlying mucosa. Note thickening and chronic inflammation of submucosa (× 100).

Pathologic findings: The kidney weighed 143.0 grams and measured 11.5 cm × 6.5 cm × 2.0 cm. The reddish-brown cortical surface showed numerous hemorrhagic foci which varied in diameter from 0.1 cm to 0.5 cm. At its upper pole, there was a 1.0 cm cortical cyst containing clear serous fluid. The renal vessels were anatomically normal in position. On section, there were foci of submucosal hemorrhage in the middle and lower calyces and the pelvis (Fig. 2). The renal parenchyma except for small hemorrhagic areas in the cortex was not remarkable.

Microscopic examination revealed small fresh cortical infarcts. Corresponding to the gross hemorrhages in the pelvis and middle and lower calyces there were subepithelial hemorrhages with elevation of the overlying mucosa (Fig. 3). The lamina propria in these areas showed moderate thickening, mild inflammation, and moderate dilatation of lymphatic channels. Also present were peripelvic hemorrhage involving the fat, mild focal interstitial nephritis and moderate arteriosclerosis of the renal vessels (Fig. 4).

Case 2: A 57-year-old Negro man entered Beth Israel Medical Center with a ten-day history of painless gross hematuria. Hesitancy and frequency of urination and hematuria had occurred four times during the past six months. He had gonorrhea in 1922. The blood pressure on admission was 125/90. Laboratory findings revealed numerous red and white blood cells in the urine. Remaining laboratory profiles, including that for sickle-cell anemia, were nega-

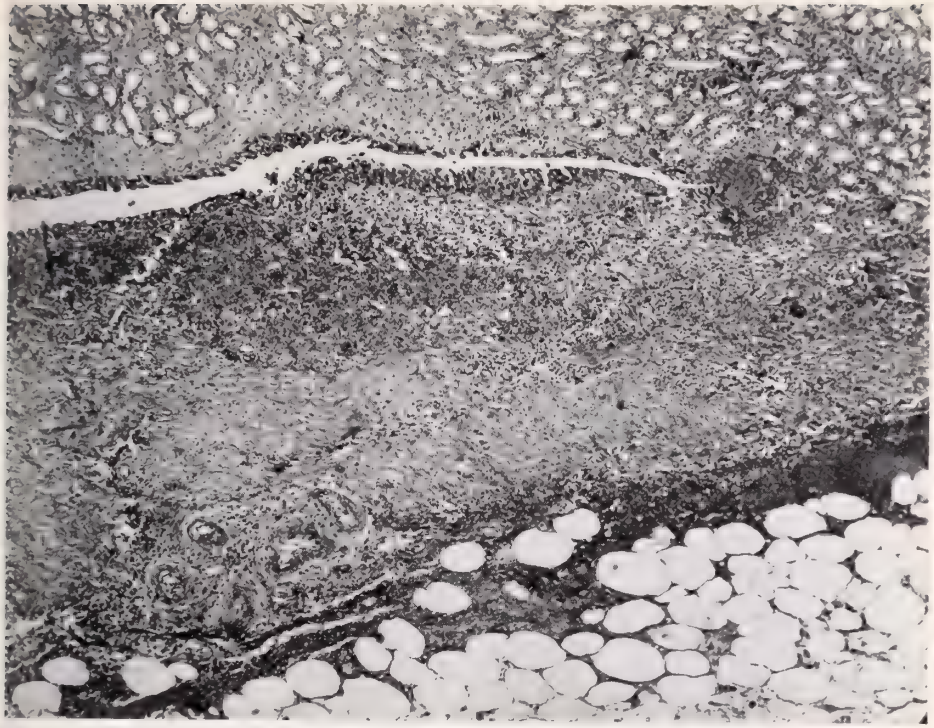

FIG. 4. Section of kidney showing submucosal and peripelvic hemorrhages (× 100).

tive. The clinical impression was that of painless hematuria due to renal or bladder tumor. Cystoscopic examination revealed moderate prostatic enlargement and a left retrograde pyelogram showed grade II dilatation of the calyces and ureters and a double collecting system (Fig. 5). No calculus was demonstrable. Aortography the following day showed a large area of diminished vascularity in the perihilar region which in the nephrogram phase had the beak-like extension characteristic of a renal cyst (Fig. 6). The inferior border of the avascular zone appeared to support the ureter, and was situated directly in the medial aspect of the kidney. A slight increase in vascularity was also present lateral to the avascular area. However, no definite "tumor vessels" were seen. The impression was that of a large avascular area in the medial aspect of the left kidney, possibly a cyst; a small pelvic neoplasm lateral to the cyst had to be excluded. With these roentgen findings, a total nephrectomy was performed on the fifth day of hospitalization.

Pathologic findings: The kidney weighed 250.0 grams and measured 14.0 cm × 7.5 cm × 3.5 cm. Fetal lobulations were discernible and a renal cortical cyst measuring 2.5 cm was present in the midportion of the kidney. On section, the renal pelvis was bifid. Fresh hemorrhages were seen in the submucosae of the pelvis and inferior calyx measuring from 0.2 cm. to 1.7 cm in diameter (Fig. 7). There was no direct communication between the cortical cyst and the outflow tract. The renal vessels were not grossly remarkable. Microscopic examination revealed subepithelial hemorrhages in the pelvis and inferior calyx and peripelvic hemorrhage (Fig. 8). There was moderate chronic inflammation in the lamina propria of the renal pelvis and a small fresh cortical infarct (Fig. 9).

Case 3: A 42-year-old Haitian woman was admitted to Beth Israel Medical Center for gross hematuria of two weeks duration which was associated with occasional left flank pain. She denied any pertinent urologic history and aspirin ingestion. Physical examination

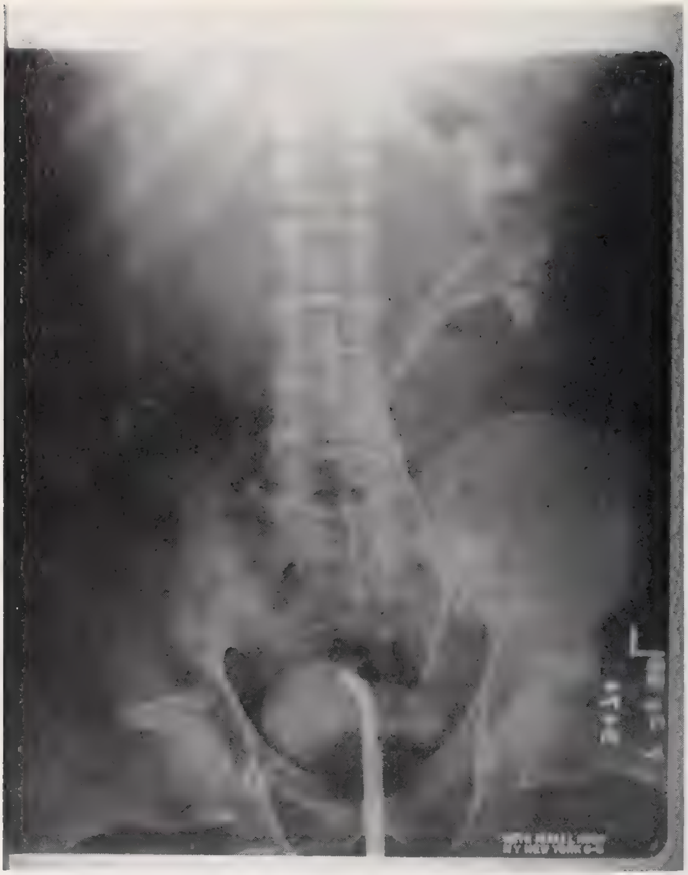

FIG. 5. Retrograde pyelogram showing double collecting system and dilatation of the calyces and ureters.

revealed an obese female with a blood pressure of 120/80. Mild costovertebral angle tenderness was present on the left side.

Laboratory data: The urine had a specific gravity of 1.009 and numerous red blood cells and 2 to 3 white blood cells per high power field. The hemoglobin was 11.6 grams and the hematocrit 35.2 percent. An intravenous pyelogram revealed good function and good visualization of both kidneys and collecting systems. Cystoscopy and retrograde pyelography on the third hospital day revealed a gross bloody efflux from the left ureteral orifice and irregularities and non-filling of the lateral portion of the left lower calyceal system (Fig. 10). The urologic impression was that of a possible angiomatous lesion of the calyx.

Hospital course: During her hospitalization the hemoglobin fell to 11.2 grams; 2 pints of blood were administered. A coagulation profile prior to transfusion was normal. A selective left renal angiography revealed no abnormalities to explain the gross hematuria. She was treated with a series of silver nitrate irrigations via a retrograde catheter. The hematuria disappeared and the patient was discharged after 26 days of hospitalization. However, 18 days later gross hematuria associated with mild left flank pains recurred. Cystoscopy and retrograde pyelography again revealed "bloody efflux from the left ureteral orifice originating from the left renal pelvis." In addition, a filling defect of the left lower major renal calyx was seen. A repeat left renal angiography showed an area suggestive of a small hemangioma and a postoperative diagnosis of possible angiomatous lesion in the pelvis or

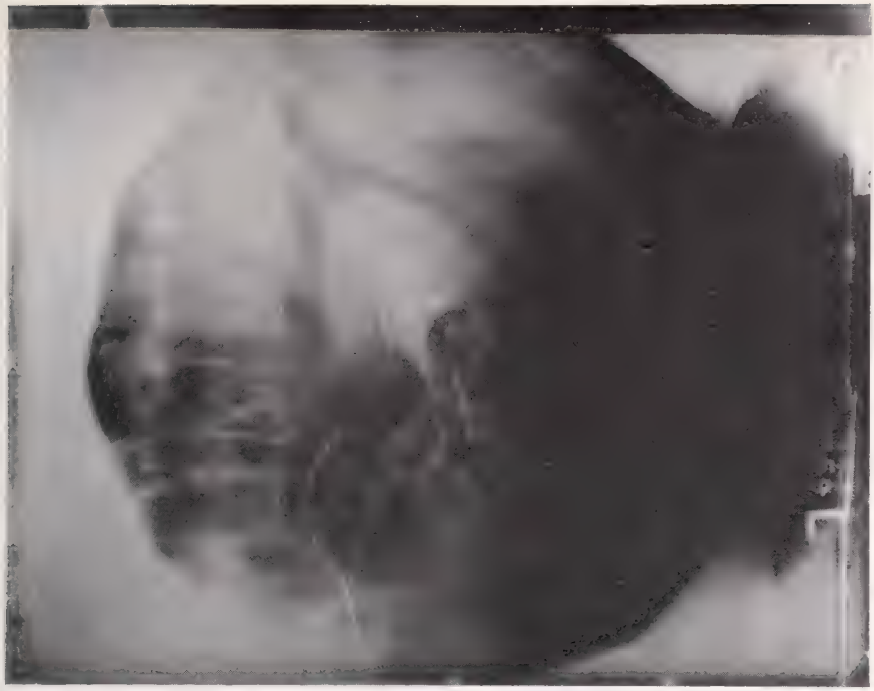

FIG. 6. Aortogram showing an avascular area with beak-like appearance and increased vascularization.

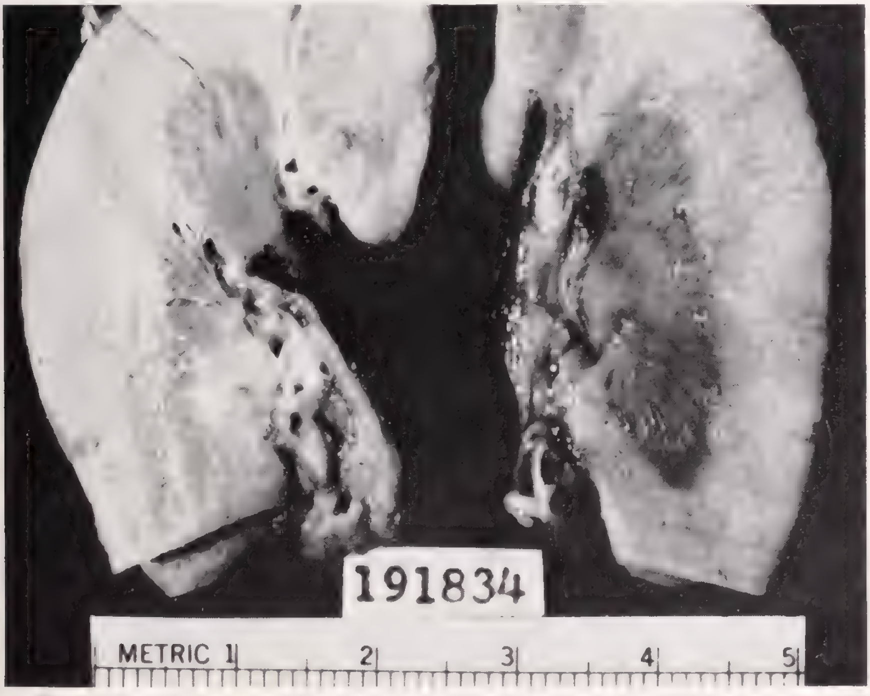

FIG. 7. Fresh submucosal hemorrhages of the renal pelvis and inferior calyx.

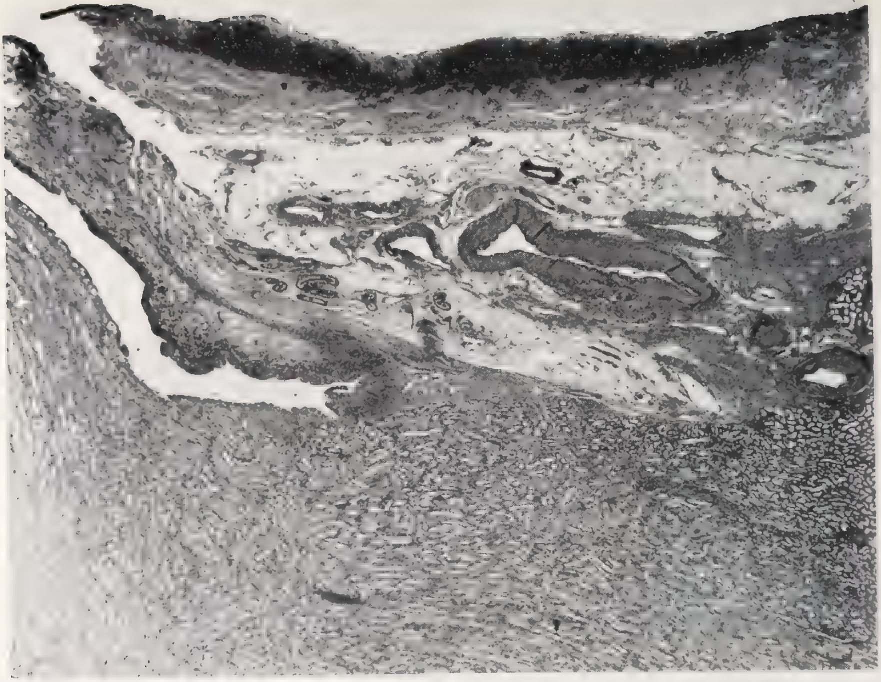

Fig. 8. Section through renal pelvis showing subepithelial hemorrhage with elevation of mucosa (× 100).

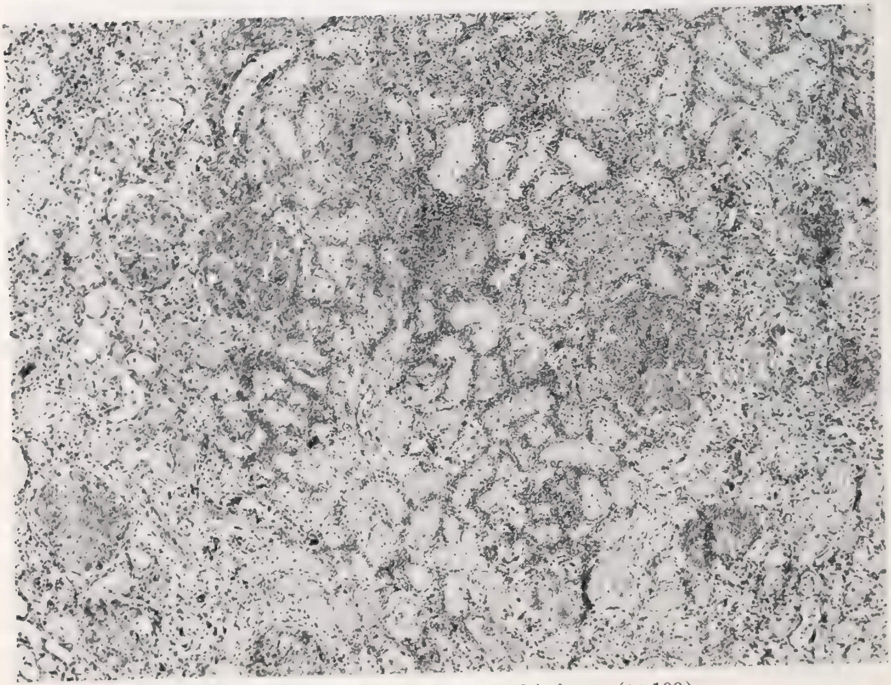

Fig. 9. Small fresh renal cortical infarcts (× 100).

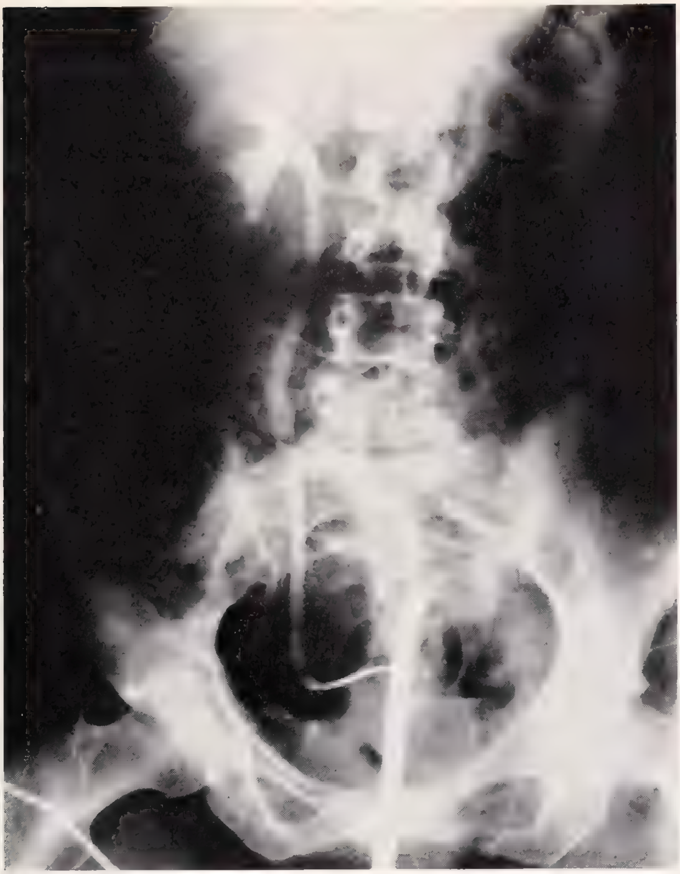

FIG. 10. Irregular and non-filling of the lateral portion of lower calyceal system.

left lower major renal calyx was made. On the fourth day following her second admission, a left renal exploration with partial resection of the lower pole was performed. Her post-operative course was uneventful and she was discharged 17 days later with an intravenous pyelography showing a well-functioning left kidney.

Pathologic findings: The resected left lower pole weighed 18.0 grams and measured 5.0 × 3.5 × 1.5 cm. Deep stellate scars and a broad scar were present on the cortex. On section, the corticomedullary junction was well delineated; submucosal hemorrhages were seen in the pelvis and inferior calyx. As in the preceding two cases, subepithelial pelvic and peripelvic hemorrhage were seen on microscopical examination of the kidney.

Discussion

Subepithelial hemorrhage of the renal pelvis simulating neoplasm originally described by Antopol and Goldman, is a pathologic entity which has received little attention in the literature. This entity may occur more frequently but the possibility of overlooking the lesion if the hematuria goes unnoticed or the lesion is not included in the differential diagnosis of hematuria should be considered. As seen in Table I, the majority of cases, including those of Antopol and Goldman, peculiarly involved the right kidney (7 of 10 cases) and affected

TABLE I

Previous Reported Cases in Literature

Case	Age	Sex	Kidney	Subepithelial hemorrhage	Peripelvic hemorrhage	History of trauma	Congenital abnormality
1	25	M	Right	+	+	+	Extrarenal pelvis
2	58	F	Left	+	+	−	—
3	53	M	Right	+	+	−	—
4	33	F	Right	+	+	−	Faulty insertion of ureter
5	30	F	Right	+	+	−	Bifid pelvis Double ureter
6	35	F	Right	+	+	+	—
7	39	F	Right	+	+	−	Aberrant vessel Extensive fetal lobulation
8	42	F	Right	+	+	−	—
9	57	M	Left	+	+	−	Bifid pelvis Fetal lobulations
10	42	F	Left	+	+	−	—

primarily females (7 of 10 cases). Five were associated with congenital malformations, and two with a history of trauma, which in one patient was not severe. There was no relationship to the number of pregnancies or occupation. The ages of the patients ranged from 25 to 58 years. The relative frequent involvement of the right kidney could be attributed to its greater mobility. Trauma, even though mild, as in case 6, could have triggered the onset of the hemorrhage since, as mentioned in the original report "the pelvis and hilar blood vessels are poorly supported in the sinus of the kidney by loose connective tissue and would, therefore not require more than slight trauma, even the inertia of the kidney with sudden changes in body motion or position, might be sufficient to produce tears of the smaller vessels in this region."

The constant radioclinical manifestations of this lesion consist of gross or microscopic hematuria and a filling defect in the renal pelvis occurring in a healthy individual, often with a history of trauma or sudden change in position or movement velocity. In case 3, the selective angiographic diagnosis of hemangiomatous lesion indicates the possible value of this diagnostic procedure. Microscopically, the subepithelial hemorrhage is associated with peripelvic hemorrhage, occasionally, with fresh superficial small cortical infarctions, and small subcapsular hemorrhage. These superficial cortical infarcts are most likely due to injury of the suprarenal and capsular vessel and in some cases to aberrant vessels (1).

With diagnosis of this lesion, observation without surgical intervention is indicated. Case 3 underwent partial nephrectomy with excellent results and return of good renal function eighteen days postoperatively. It is unfortunate that at present there is no adequate way to diagnose this lesion. The diagnosis of the lesion is disappointingly difficult if not impossible to make, as exemplified by the original cases and the ones now reported; a correct preoperative diagnosis was never made in any of them.

With recognition and better understanding of this pathologic entity through the development of more sophisticated and accurate radiographic techniques, it is hoped that a conservative and even nonsurgical approach to the treatment of this disease might be considered, thereby saving an occasional normal kidney.

Summary

Three additional cases of subepithelial hemorrhage of renal pelvis simulating neoplasm (Antopol-Goldman lesion) are reported, and the original cases briefly reviewed. The difficulty in arriving at a correct preoperative diagnosis is discussed. If diagnosed, management of this lesion should be conservative.

Acknowledgment

We wish to acknowledge the radiologic interpretations of Abraham Geffen, M.D. and Maurice Goodgold, M.D., Department of Radiology, Beth Israel Medical Center.

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Drusen of the Optic Nerves and Meningioma: A Case Report

PETER HERMAN BEN-ZUR, M.D. AND THEODORE W. LIEBERMAN, M.D.

Drusen of the optic nerves, if unrecognized, may lead to extensive unwarranted neurologic evaluations. On the other hand, their recognition as benign lesions may cause important signs and symptoms to be dismissed as insignificant. This paper presents a patient with the uncommon and chance association of drusen of the optic discs with an intracranial meningioma. It discusses the diagnostic problems associated with drusen of the optic nerve head.

Case Report

A 44-year-old white woman was hospitalized in July, 1969 for a neurologic evaluation because of one seizure episode. Two and one-half weeks before admission the patient awoke in the middle of the night and was aware of an uncontrollable rhythmic movement of her upper extremities and head. According to the patient's husband, she did not respond to his questions, lost consciousness for several minutes, breathed heavily, and foamed around the mouth. No history of a neurologic deficit following the seizure could be elicited. The patient claimed complete recollection of events before loss of consciousness.

The patient was subject to recurrent moderately severe diffuse headaches since 1965 for which she took aspirin or chlordiazepoxide. During the year preceding admission she described "difficulty in finding words," and six months before admission had one episode of "dimness" of vision in the right eye lasting one minute.

Significant history included the presence of a heart murmur since childhood. She was treated for hypertension with a combination drug of methyclothiazide and deserpidine for the year preceding hospitalization.

Examination: Physical examination at the time of admission revealed a healthy appearing woman with a blood pressure of 140/80 and a regular pulse. There was a IV/VI systolic decrescendo blowing murmur, heard best over the apex of the heart with radiation to the axilla.

On neurologic examination the patient was alert, cooperative and had no communication disorder. However, she showed slight difficulty with immediate retention. The remainder of the neurologic examination was normal.

Ophthalmologic examination was normal except for the optic discs which were elevated and filled with yellow-white, glistening, round bodies which overlapped the disc margins producing an irregular edge. The retinal vessels coursed over the surface of the drusen with some of the fine vessels being displaced by these structures.

On a more recent eye examination on December 29, 1970 the visual acuity was found to be 20/20 in each eye without correction. The visual fields showed bilateral enlargement of the blind spots. The superior nasal field of the left eye was depressed (Fig. 1). The fundi appeared as originally described (Figs. 2 and 3). A fluorescein angiogram showed a characteristic pseudofluorescence of the drusen even before injection of the fluorescein dye (Fig. 4a). There was no evidence of edema of the nerve head in late (10 to 20 minutes) postinjection photographs (Fig. 4b).

Laboratory Data: Chest x-rays (PA and lateral) were suggestive of mitral disease. An electrocardiogram was normal.

An electroencephalogram was normal. Brain scan showed increased accumulation of the technecium-99m isotope in the left fronto-parieto-temporal region.

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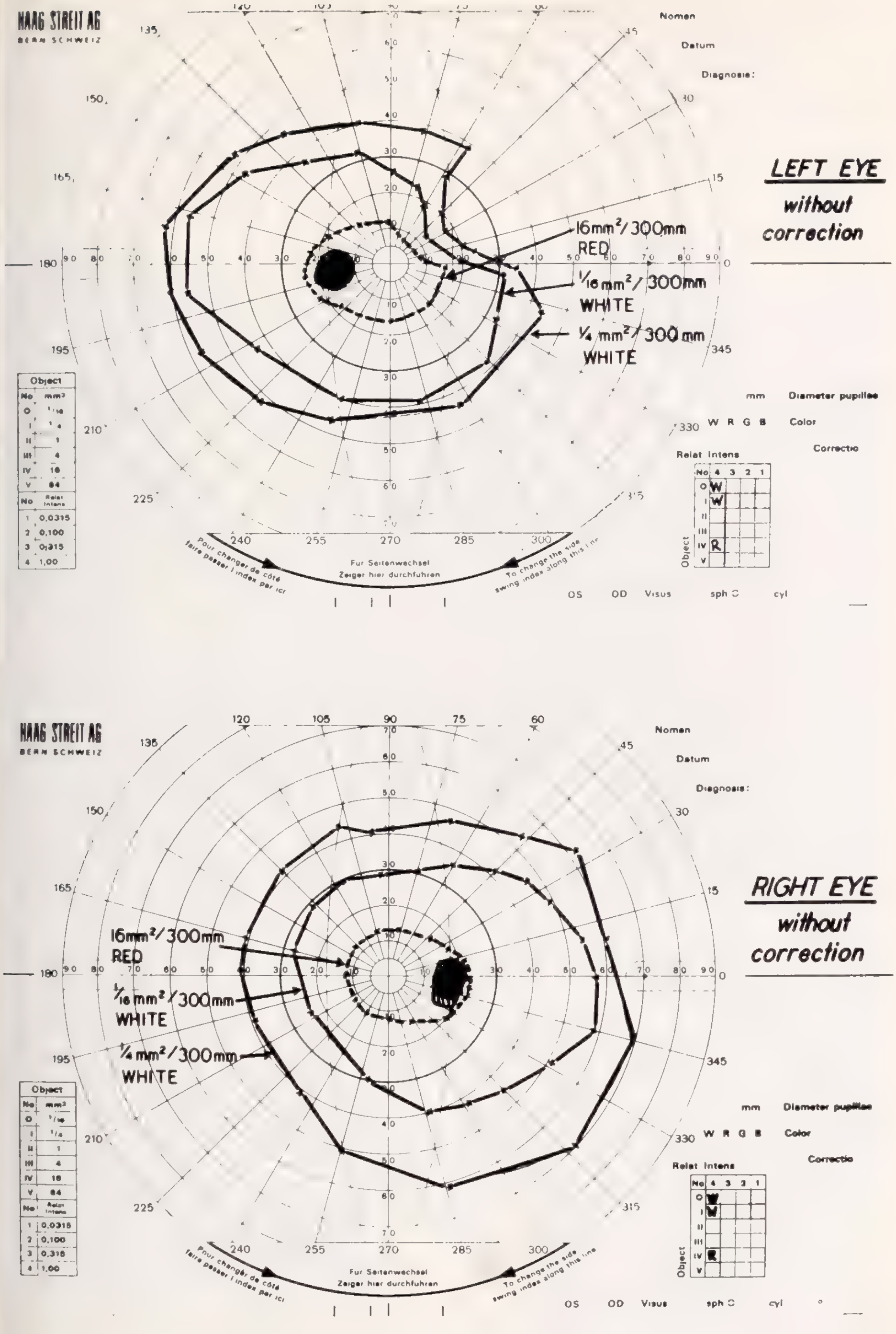
HAAG STREIT AG
BERN SCHWEIZ
Nomen
Datum
Diagnosis:
LEFT EYE
without correction
16mm²/300mm RED
1/16 mm²/300mm WHITE
1/4 mm²/300 mm WHITE
Object
No mm²
Relat Intens
0,0315
0,100
0,315
1,00
mm Diameter pupillae
W R G B Color
Correctio
Fur Seitenwechsel Zeiger hier durchfuhren
Pour changer de côté faire passer l'index par ici
To change the side swing index along this line
OS OD Visus sph cyl
RIGHT EYE
without correction
16mm²/300mm RED
1/16 mm²/300mm WHITE
1/4 mm²/300mm WHITE

FIG. 1. Goldmann visual fields show bilateral enlarged blind spots and a left superior nasal defect.

Skull x-rays were normal. A left carotid angiogram (Fig. 5) showed a stain suggestive of a mass in the suprasylvian region. It was superficially located around the inner table of the calvarium, posterior to the coronal suture. Two meningeal branches ended abruptly in the area of the stain. A pneumoencephalogram (PEG) showed a few areas of cortical atrophy most pronounced in the right frontal area. Cerebrospinal fluid withdrawn during the PEG had a protein of 90.5 mg/100 ml, and sugar of 56 mg/100 ml. No cells were present.

Tomograms of the skull showed thickening of the inner table in the left temporo-parietal region above the squamous suture corresponding to the increased stain seen on angiography (Fig. 6).

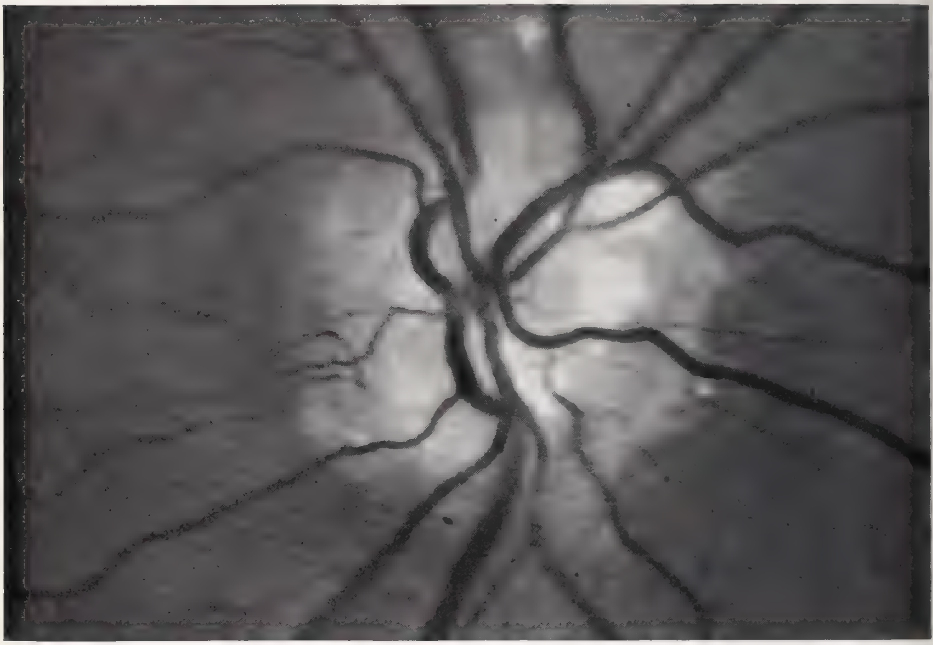

FIG. 2. Reproduction of Kodachrome photograph of patient's right optic disc showing drusen, which are not as well delineated as the drusen in the left disc (Fig. 3).

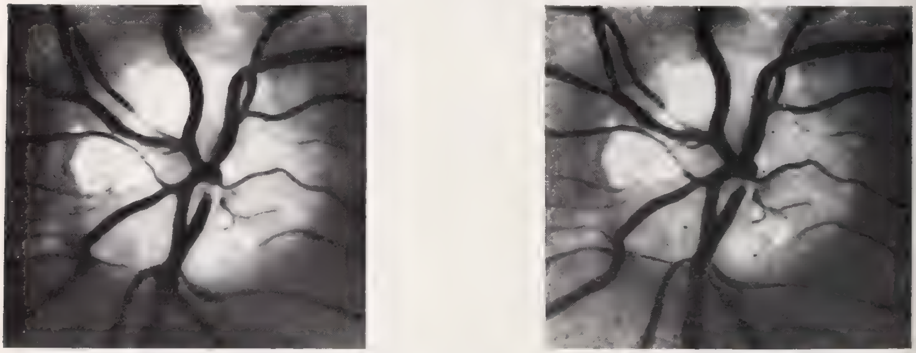

FIG. 3. Stereophotographs reproduced from Kodachrome photographs of patient's left optic disc.

Course: Since the findings were consistent with a meningioma "en plaque," it was decided to treat the patient conservatively with 30 mg phenobarbital three times daily for prevention of further seizures.

For one year the patient was free of seizures, headaches, and visual complaints. On two consecutive occasions her brain scan has been similar to the one in the hospital. In December, 1970 she reported two seizures, both of which consisted of rhythmic turning of the head to the right without loss of consciousness.

An ophthalmic examination of the patient's four offspring (sons) revealed no evidence of drusen of the optic nerve. One son, born prematurely and subjected to incubator oxygen at birth, had bilateral low-grade retrolental fibroplasia with a partial retinal detachment in one eye.

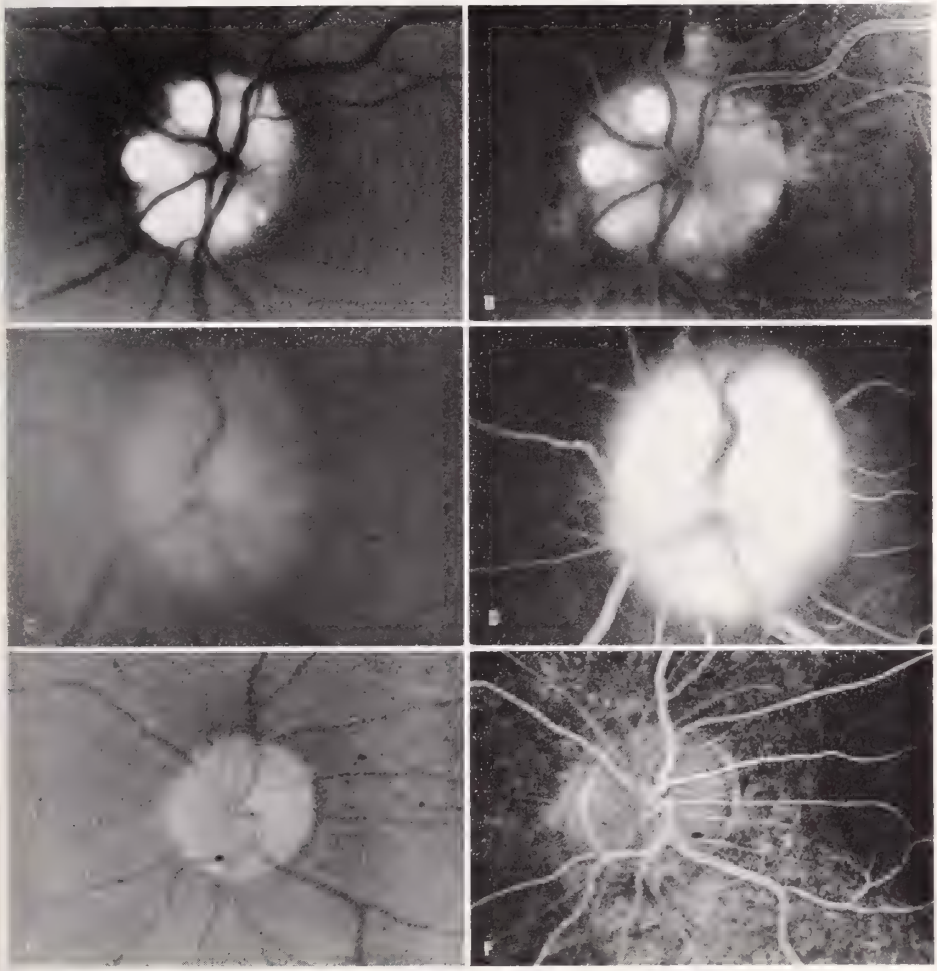

Fig. 4. Fluorescein angiograms obtained with purple exciting light (Baird-Atomic B-4 interference filter) before (a, c, e) and 10 to 20 minutes after (b, d, f) intravenous injection of fluorescein. a & b, Patient's left disc with drusen; c & d, papilledema; e & f, normal. Only drusen (a) shows pseudofluorescence before injection of fluorescein. After injection, the edematous disc (d) shows increased fluorescence and leakage of fluorescein over the disc margins. The edges of the normal disc (f) and the disc with drusen (b) duplicate those seen on funduscopy or as seen on ordinary photographs (compare Fig. 4b with Fig. 3).

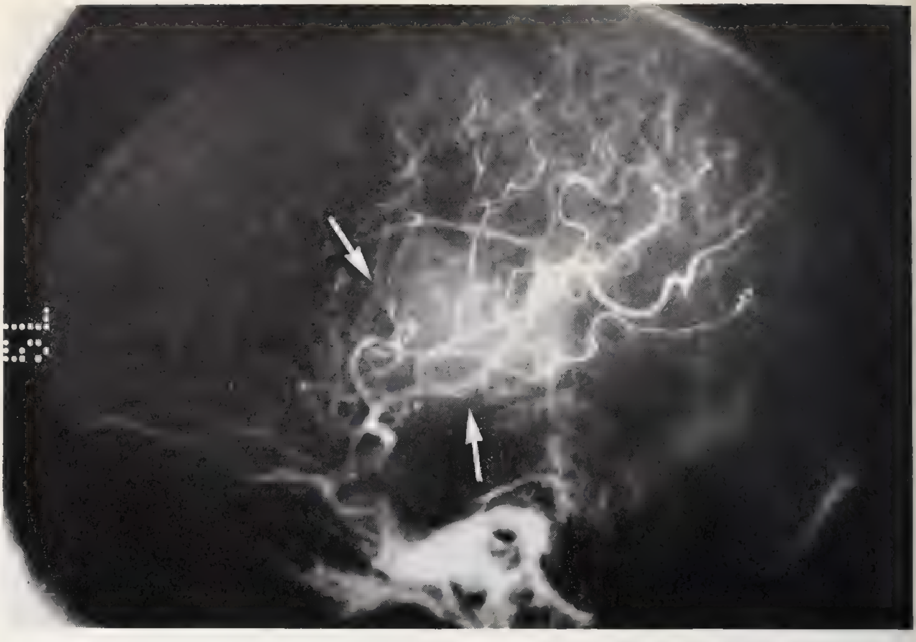

FIG. 5. Left carotid angiogram shows stain in suprasylvian region.

Discussion

Drusen of the optic nerves were first described histologically by Muller (1) in 1858 and ophthalmoscopically by Liebreich (1) in 1868. On hematoxylin and eosin stained histologic sections, drusen consist of eosinophilic amorphous or laminated masses which frequently calcify, becoming basophilic. They are irregularly round in shape, vary in size, and often form large conglomerates of individual nodules. They are always located anterior to the scleral lamina cribrosa, produce an elevation of the surface of the nerve head, and are more numerous in the nasal than in the temporal portion of the disc. The vessels and the axons of the optic nerve are displaced by the drusen. The axons may be interrupted. The origin of drusen is not known although they have been variously attributed as derived from degenerative products of nerve fibers, hyalin deposits of neuroglia, and as the product of displaced cells of the pigment epithelium of the retina.

The incidence of drusen is approximately 3.4 per 1000 people as determined by a study of 3,200 subjects visiting an ophthalmologist for reasons unrelated to drusen (1). Their incidence is equal in both sexes, but they are uncommon in non-Caucasians (2). Although drusen of the discs are often bilateral, they may occur unilaterally in up to 28% of subjects (1).

Drusen are often familial and are considered to be transmitted as an irregular dominant trait with low penetrance. In Lorentzen's study (1) of 909 examined relatives of 49 propositi with drusen, 3.1% of the relatives were found to be affected. In a group of 218 close relatives of the same 49 subjects, 14% of the parents, 5% of the siblings, and 7.5% of the offspring had drusen.

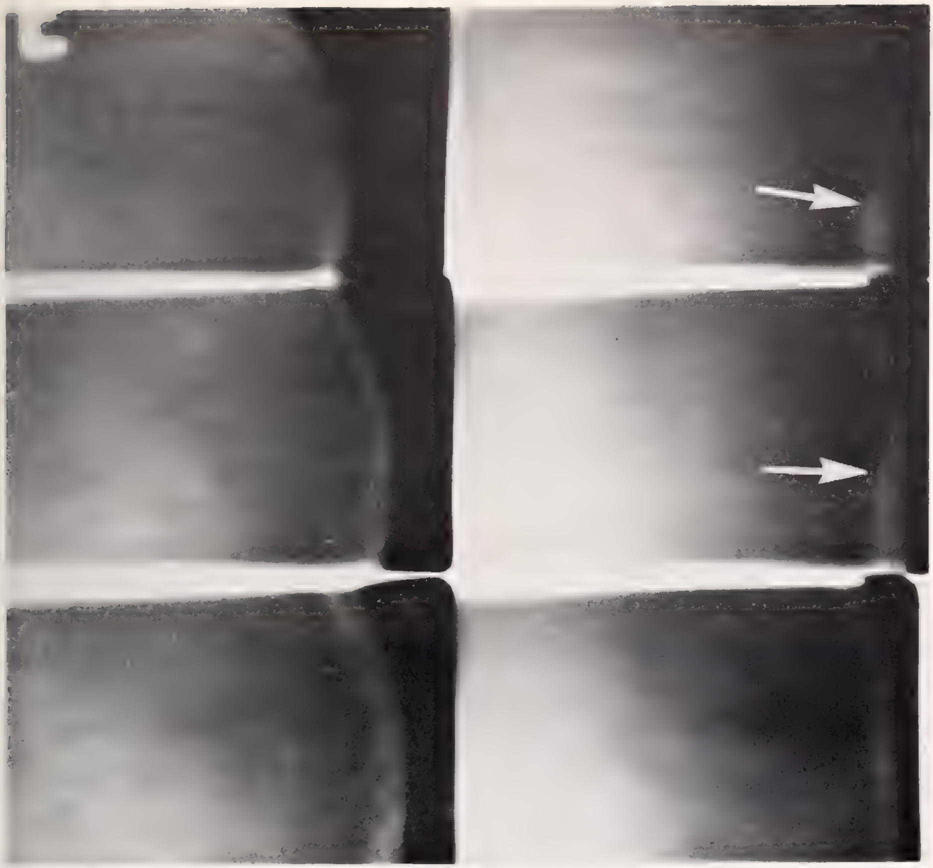

Fig. 6. Tomograms of left temporo-parietal skull shows thickening of inner table corresponding to area of angiographic stain.

Drusen have been found associated with retinitis pigmentosa and in pseudoxanthoma elasticum with angioid streaks. Although they were at one time considered to be a component of tuberous sclerosis (3), a picture similar to drusen of the optic nerves seen in this phakomatosis is now considered to represent an astroglial hamartoma (4). Of interest to neurologists is the fact that drusen may resemble the exudates found in true chronic papilledema (5) or the hyaline-like bodies seen in postpapilledema optic atrophy.

From a neurologic viewpoint, drusen may present difficulties in diagnosis since they may be confused with papilledema (1, 2, 6). In the fully developed form as presented in this case report, they cause no problem. However, when the drusen are more deeply buried or less massive or numerous, they represent one form of pseudopapilledema. This is especially considered true in children, where the drusen may still lie below the surface of the disc (2, 6). Viewing the optic disc with the penumbra of the ophthalmoscope light which is projected onto the disc edge may bring out the concentric bodies within the substance of the disc. Slit lamp examination of the disc with the use of special lenses may also delineate drusen. In the presence of drusen the disc margins are often irregularly scalloped. The vessels ride on top of the disc substance and are not obscured by edematous semi-opaque nerve tissue as seen in papilledema. The veins remain of normal caliber and splinter hemorrhages are uncommon (1). The blind spot is enlarged, but does not show a significant increase in size when smaller test objects are used, as is commonly the case in papilledema. Where all of these examinations are equivocal for the presence of drusen, examination of the relatives may be useful.

In attempting to determine if true papilledema exists or is associated with drusen, fluorescein angiography may be useful. Figure 4 shows the fluorescein angiogram (before, and 10 to 20 minutes after the injection of the dye) in a disc with drusen (present case), a disc with papilledema, and in a normal disc. Drusen show a pseudofluorescence before injection which is not seen either in papilledema or in normals. After injection of the fluorescein, the disc with drusen shows an irregular density of the fluorescein on the disc surface and an irregularity of the margins of the fluorescence which exactly duplicates those seen on funduscopy or on ordinary photographs of the disc (compare Fig. 4b with Fig. 3). In true papilledema there is marked fluorescence of the optic disc surface and spillage of the fluorescein over the disc margins. Unfortunately, in very early edema, fluorescein angiography may be difficult to interpret.

Loss of visual acuity, if unassociated with retinal pathology, such as retinitis pigmentosa, angioid streaks, or subretinal or vitreous hemorrhages (7), should be investigated. In Lorentzen's series of 70 patients with drusen of the optic nerve (121 eyes), only six patients had vision less than 20/30 (1). Five had unilateral nonprogressive decrease in vision, all of which were attributed to an amblyopia associated with refractive or strabismic problems. One subject had bilateral poor vision associated with angioid streaks. This is contrasted to the subjects with drusen and intracranial space-occupying lesions, where according to Lorentzen's compilation of nine such reported cases, seven had reduced central visual acuity. One had no details given as to the acuity. One case had normal visual acuity with a right homonymous hemianopsia secondary to a left temporal occipital abcess. Of the seven cases with impaired vision, the acuity of three subjects was reported as being "impaired" and the four other subjects had 20/400 or worse vision in the poorer seeing eye. All seven cases had tumors either in the region of the intracranial portion of the optic nerve (one meningioma) or the chiasm (three pituitary tumors, one craniopharyngioma, one tuberculum sella meningioma, and one space-occupying lesion at the base of the brain). Drusen, without associated hemorrhages, have been infrequently cited as the cause of diminished central acuity (6, 10). Rucker and Kearns have considered loss of visual acuity as an indication for neurologic evaluation (11) and we concur with this approach.

Enlarged blind spots and nasal field defects as found in this patient are commonly associated with drusen (1). Arcuate scotomas arising from the blind spot and temporal defects also occur. However, unless the visual field defect fits distinctly into bitemporal or homonymous hemianopic patterns, a neurologic investigation is not warranted on the basis of the field abnormality itself.

Obscuration of vision as described by the patient in this report is associated with drusen of the optic nerve. Of Lorentzen's 70 cases with drusen, six patients described obscurations of vision lasting seconds to hours. It would appear that obscurations of vision are a symptom of drusen of the optic nerve, but in the older individual transient ischemic attacks from carotid disease may produce similar episodes of loss of vision.

The patient in the present report had very little consideration paid to her optic discs in regard to her neurologic work-up. She represents that group of patients where nonophthalmic considerations led to a complete evaluation. A significant number of patients with drusen of the optic nerves have been reported to have neurologic problems unrelated to their drusen. This high incidence may be due to the method of gathering case material, or because of the authors' interest in neuro-ophthalmology (1, 2). Hoyt (2) suggests conservative management (repeated examination of the optic discs and visual fields for enlargement of the blind spot) of patients with drusen of the optic nerve, unless the neurologic symptoms and signs warrant more extensive evaluations.

Intracranial space-occupying lesions are not common in the presence of optic nerve drusen. Aside from the cases referred to in this report, only a few other undetailed references of this combination of lesions can be found (10, 12). The association of these two conditions is probably a chance occurrence. It is of interest that most of these intracranial tumors have involved the visual pathways, but the series of tumors reported may be biased in that all reports have appeared in the ophthalmic literature.

Summary

A case of bilateral optic nerve drusen associated with meningioma was studied. In the presence of drusen of the optic nerve the following ophthalmologic considerations warrant further neurologic investigation: 1) progressive loss of central visual acuity unexplained by retinal pathology, 2) homonymous hemianopic or bitemporal field defects, and 3) evidence of papilledema. As in this case, significant neurologic symptoms warrant an appropriate work-up irrespective of the known benignity of drusen and their chance association with intracranial tumors.

Acknowledgment

We thank Joseph Ransohoff II, M.D., Professor and Chairman, Department of Neurosurgery, New York University for allowing us to study and report this patient. Donald Wong, B.A., and Muriel Laban performed the photography.

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Levodopa-Induced Dyskinesia in the Normal Rhesus Monkey

ROBERT J. MONES, M.D.

Introduction

Levodopa therapy has been a great advance in the treatment of Parkinson's disease. L-dopa-induced dyskinesias are one of the most important and frequent problems when L-dopa is given chronically to patients. The dyskinesias occur in perhaps fifty percent of the patients being treated with L-dopa and are the limiting factor in the patient's improvement in at least one-quarter of the patients started on L-dopa therapy. The cause of dyskinesia during L-dopa therapy is not understood. This paper is a presentation of a model in the normal rhesus monkey of L-dopa-induced dyskinesia.

Methods

In ten short experiments using three different monkeys, L-dopa has been injected in the intraperitoneal cavity. In the initial three experiments (see Table I), L-dopa in an initial dosage of 200 mgs/kg and then at 400 mgs/kg was injected in a saline suspension of 15 cc. The animals were normal Rhesus monkeys who had been fasted overnight. They were observed for at least six hours after the injection of L-dopa in a laboratory chair which holds the animal by means of a neck collar and a hip bar. The animals were free to move their arms, legs, mouth, and head. After the intraperitoneal injection of L-dopa, the animals were observed for the next six hours and movies were taken at thirty-minute intervals. In experiment numbers 4 to 10, various amounts of L-dopa were injected simultaneously with alpha methyl dopa hydrazine (MK-486). The MK-486, which is a dopa decarboxylase inhibitor, was injected in doses between 20 mgs/kg and 80 mgs/kg. The animals were observed again for six hours in the manner described above and frequent movies were taken.

Results

In the initial three experiments, in which L-dopa alone was injected into the intraperitoneal cavity of the monkey, no definite abnormal movements were noted, although the animals became somewhat hyperactive about an hour after the injection. In experiment numbers 4 and 5, in which less than 40 mgs/kg of MK-486 was injected with the L-dopa, the monkeys did not have any bizarre abnormal movements, although the hyperactivity occurred as described in the first three experiments.

In experiments numbers 6 to 10, 40–80 mgs/kg of MK-486 was injected simultaneously with the L-dopa. In all five of these experiments, involving three different animals, abnormal involuntary movements were noted. The monkeys

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TABLE I

Summary of Experiments

Experiment No.	Date	Monkey No.	Animal weight	Drug dosage I.P.				Dyskinesia	Results
				L-dopa		MK-486*			
				mgs	mgs/kg	mgs	mgs/kg		
1	6-02	638	4.3 kg	860	200	0	0	0	Recovered
2	6-09	638	4.3 kg	1720	400	0	0	0	Recovered
3	6-23	636	4.2 kg	1680	400	0	0	0	Recovered
4	7-14	636	4.2 kg	1050	250	50(oral)	12	0	Recovered
5	8-04	636	4.2 kg	1680	400	80	20	0	Recovered
6	8-11	636	4.2 kg	1680	400	340	80	+	Recovered
7	9-15	638	4.3 kg	1720	400	344	80	+	Recovered
8	9-22	671	2.2 kg	880	400	176	80	+	(Died)
9	10-06	638	4.3 kg	1290	300	260	60	+	Recovered
10	10-13	636	4.2 kg	840	200	170	40	+	Recovered

* MK-486—alpha methyl dopa hydrazine (Merck Sharp & Dohme).

first were noted to become hyperactive and excited about one-half hour after the injection. Constant movements of the extremities, hips, and shoulders were noted and chewing and nibbling movements of the tongue, mouth, and lips were seen. Forty-five minutes after the injection, definite bizarre abnormal movements were noted in the mouth, tongue, jaw, and neck (see Figure 1). Constant jaw opening was noted, with protrusion of the tongue and neck in a bizarre fashion. The animal became more excited, hyperactive, and many choreiform movements were seen in the limbs. The abnormal movements were maximal at about one and one-half hours after the injection and then slowly waned until they disappeared at about three hours. The pupils were of normal size throughout this period and they reacted to light. No lid retraction was noted. The eye movements were normal, the monkey was alert and reacted to stimuli such as food, noise, and threatening gestures in a normal manner.

The bizarre abnormal movements were similar in all respects in experiment numbers 6 to 10. Monkeys number 636 and number 638, weighing over 4 kg, recovered completely from the multiple injections and, at present, are in a normal state. Monkey number 671, who weighed 2.2 kg, responded in the manner described above; however, three hours after the intraperitoneal injection of L-dopa and MK-486 and after the dyskinesia had stopped, the animal was noted to become weak, appeared to be in shock, and died one hour later or four hours after the injection of drugs. The postmortem examination of this monkey revealed no gross abnormalities in the peritoneal cavity, except for a minimal amount of nonabsorbed L-dopa and MK-486 powder. The brain was hyperemic, but no hemorrhages or gross abnormalities of the brain were noted and the other organs were grossly normal.

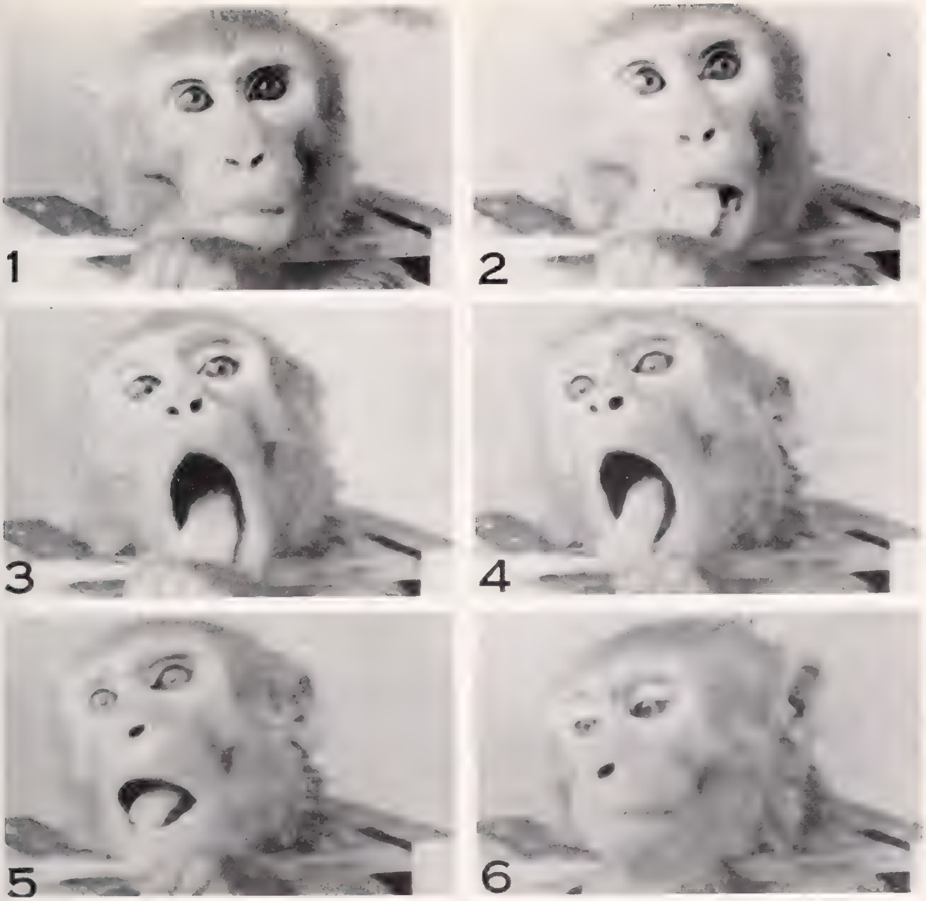

Fig. 1. Six frames of a two-second film strip in experiment number 6 are shown 90 minutes after the injection of L-dopa/MK-486 combination. Identical repetitive abnormal movements occurred for at least two hours in Experiments 6 to 10.

Discussion

The pathophysiology of clinical dyskinesia in man is a poorly understood phenomenon. One reason for our ignorance on the subject is a lack of a good experimental model for study. Previous investigators have produced experimental dyskinesia in the Rhesus monkey by making lesions in various parts of the brain, including the ventral tegmentum of the midbrain (1, 2), or the subthalamus (3, 4). L-dopa alone has been injected intraperitoneally in the normal Rhesus monkey and hyperactivity and abnormal movements have been described (5).

The advent of L-dopa therapy in Parkinson's disease has made dyskinesia an important subject because the most common cause of dyskinesia in clinical neurology today is L-dopa administration. In the Parkinson patient treated with

L-dopa, mouth, tongue, jaw, and neck movements are the most common abnormality, although trunk and limb movements also occur. At present, there is no definite method to eliminate the side effects of L-dopa as described except by reducing the drug, which frequently diminishes the efficacy of the therapeutic response that the patient enjoys (6–10).

The use of dopa decarboxylase inhibitor (MK-486) with L-dopa has not eliminated the problem of dyskinesia in the Parkinson patient. Dopa decarboxylase inhibitors have been used clinically for the past three years to reduce the breakdown of L-dopa to dopamine in the extracerebral areas of the body. The inhibitors themselves have no obvious effect on the brain in the dosages given. Although less L-dopa is needed for a clinical response when the dopa decarboxylase inhibitors are used, the incidence of dyskinesia increases with the use of this substance (11–13). The production of a transient reproducible L-dopa/MK-486-induced dyskinesia model is, therefore, of great interest to neurologists who are treating Parkinson's disease patients. This model may also be of value as a tool to understand spontaneous dyskinesias such as chorea and dystonia.

The production of L-dopa-induced dyskinesia in the normal primate has an important meaning as it has been thought that non-Parkinson's disease patients do not develop dyskinesia when on L-dopa. In a number of non-Parkinson's disease patients with various diseases of the nervous system, L-dopa has been given, but no dyskinesias have definitely occurred (10). The production of dyskinesias by the injection of L-dopa and MK-486 in the normal primate implies that the phenomenon of L-dopa-induced dyskinesia can occur in the normal primate and that the pathology of the Parkinson brain is not necessary for its production.

Conclusion

The intraperitoneal injection of levodopa and alpha methyl dopa hydrazine in the normal Rhesus monkey has produced a predictable transient dyskinesia which is similar to the L-dopa-induced dyskinesia seen in human Parkinson patients. This model of L-dopa-induced dyskinesia in the normal primate should be of great help in the future for the elucidation of the cause and treatment of dyskinesias.

Acknowledgment

I wish to thank Drs. Tauba and Pedro Pasik for their advice and help on this project. Dr. Marvin Jaffe of Merck, Sharp, and Dohme Research Laboratories, West Point, Pennsylvania, supplied the MK-486 for this study.

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CLINICO-PATHOLOGIC CONFERENCE

Reticulum Cell Sarcoma and Hypercalcemia in an Elderly Woman

FRANKLIN M. KLION, M.D., EDITOR

Case Report

An 82-year-old Negro woman was admitted to The Mount Sinai Hospital for the first time because of hoarseness, dysphagia, and loss of weight for 10 months. Thirty-five years ago she developed diabetes mellitus, and subsequently was managed with diet and sulfonylurea therapy. She noted vague generalized bone pain for approximately one year. There was no history of polyuria, abdominal pain, nausea, fractures, renal disease, hypertension, milk or alkali ingestion, or frequent infections.

She was an elderly, obese woman. The blood pressure was 110/80, pulse 78/min and regular, respirations 18/min, and temperature 98.4°F. An 8-cm mass in the left tonsillar area extended into the soft palate, left nasopharyngeal wall, left side of the vallecula, and base of the tongue. Multiple enlarged left jugular nodes were palpated. The thyroid gland was normal in size. Examination of the eyes revealed an arcus senilis. Fine rales and rhonchi were found in the right lower lung field. The heart and breasts were normal. The abdomen was slightly protuberant and soft. The spleen and liver were not palpable. The uterus was enlarged, nodular, and a 14 x 13 x 10 cm, irregularly shaped, freely movable mass was palpated in the left adnexa. The right adnexa was normal. There was mild edema of the ankles. The neurologic examination was normal. The hemoglobin was 11.9 G %, hematocrit 30%, white blood cell count 6,900/mm^3, with 62% segmented polys, 4% band forms, 29% lymphocytes, 2% eosinophils, and 3% atypical lymphocytes. The BUN was 10 mg %, glucose 200 mg %, total protein 7.5 G %, albumin 4.0 G %, calcium 13.5 mg %, phosphorus 2.1 mg %, alkaline phosphatase activity 52 Iu/ml, uric acid 4.0 mg %, LDH 450 Iu/ml, SGOT 30 Iu/ml, and bilirubin 1.0 mg %. The urine specific gravity was 1.010; pH was 5.9 and contained a trace of glucose and moderate acetone. There were 2 to 3 white blood cells per high power field. A chest x-ray was normal. A skin test with intermediate strength purified protein derivative was negative. An electrocardiogram was normal.

A tracheostomy was performed on admission, and subsequently a tonsillar biopsy revealed reticulum cell sarcoma. Radiation therapy was begun on the 10th hospital day. The serum calcium ranged from 11.8 to 15 mg/100 ml, phosphorus from 1.2 to 3 mg/ml, and alkaline phosphatase activity 50 to 250 Iu/ml. The urine calcium excretion was 508 mg/L, and urine phosphorus 1.76 mg/L (approximate urine output was one liter). The serum parathormone level was 6 ule/ml. The tonsillar mass greatly decreased in size with radiotherapy, and nodes were no longer palpable in the neck. Shortly thereafter the patient became confused, weak, dehydrated, and febrile. She was treated with fluids and antibiotics, including erythromycin, ampicillin, and penicillin. The BUN rose to 63 mg % and the creatinine was 1.5 mg %. Despite continued hydration, the urine specific gravity remained 1.010 on several determinations. The patient became more obtunded and slightly edematous. The serum sodium was 143 mEq/L, chlorides 110 mEq/L, CO_2 22 mEq/L.

Sodium sulfate therapy was started with little change in serum calcium levels. X-ray film of the chest revealed bilateral pleural effusions and infiltrates in both lower lobes. The cerebrospinal fluid pressure was 80 mm/H_2O; the fluid was clear and contained 28 mg % of protein, 214 mg/100 ml of glucose, and 121 mEq/L of chlorides. The cerebrospinal fluid contained abnormal cells of possible metastatic origin. The hemoglobin fell to 7.2 G %, reticulocyte count was 6%, platelet count 35,000/mm^3, prothrombin time 13 seconds. The serum iron was 71 μG %, and T.I.B.C. 166 μG %. The stool was positive for occult blood. The serum haptoglobin test on two occasions was 158 mg % and 50 mg %; a Coombs' test and VDRL were negative. The peripheral white blood cell count was 13,500/mm^3 with 10% band forms, 78% segmented polys, 10% lymphocytes, 2% monocytes, and 2 normoblasts/100 WBC. The red cells showed anisocytosis, hypochromia, poikilocytosis, and polychromasia. The bone marrow was normocellular with erythroid hyperplasia. Myeloid cells were reduced, but the morphology and maturation were normal. The megakaryocytes were normal. No tumor cells were seen. On the 53rd hospital day, Decadron® therapy was started because of presumed hemolysis. Intrathecal methotrexate was given and therapy with leukeran and vincristine was begun.

She developed sudden difficulty in breathing and emergency bronchoscopy was performed. No obstruction was found. Two days later, on the 55th hospital day, the patient died.

Discussion

Dr. Dorothy Krieger:* Today's CPC is unusual, in that we are given the diagnosis. I shall discuss, therefore, whether this diagnosis explained the hypercalcemia. First, I would like to comment on certain statements in the protocol. The history of diabetes mellitus, I feel, is not significant, and probably was not responsible for her dehydration, nor did it contribute to her illness. Similarly, generalized bone pain is common in postmenopausal osteoporosis, and would not be unusual in an 82-year-old female.

On the basis of the history, she had none of the characteristic symptoms of hypercalcemia. There was no history of polyuria or polydypsia. Also not mentioned are changes of personality, constipation, or muscle weakness, which can also be seen in hypercalcemia. The history eliminates some other etiologies of hypercalcemia, such as hypervitaminosis D, thiazide-induced hypercalcemia (as might be seen secondary to such use in hypertension), and the milk-alkali syndrome.

The blood pressure was normal. Occasionally in the hypercalcemia secondary to hyperparathyroidism, the blood pressure is elevated and sometimes reverts to normal with treatment. The mass in the left tonsillar area was not ulcerated so that a squamous cell or adenocarcinoma of one of the retropharyngeal salivary glands would be unlikely. It could possibly be an extension of a Schmincke tumor. Roughly 12 percent of malignancies in this area are lymphosarcomatous in type, either reticulum cell or lymphosarcoma. These are typically nonulcerating lesions. Even though the patient was somewhat past the median age for a lymphosarcoma or a reticulum cell sarcoma, we certainly would not exclude this particular diagnosis, and it would represent, actually, an extranodal primary site of lymphosarcoma with some local lymph node involvement as well.

The rest of the physical examination is of interest only in that the spleen and liver were not palpable, and there was no other adenopathy, so that if the tumor was a lymphosarcoma or a reticulum cell sarcoma, there is no evidence of spread. The mass in the left adnexal region, as discussed, was probably a fibroid uterus. The mild ankle edema, in the absence of cardiac failure or hypertension, might have been due to local venous stasis. She was mildly anemic, which might be more significant in the face of the dehydration than would be expected to accompany hypercalcemia. The BUN was normal. The white blood cell count showed mild leukocytosis with a normal number of lymphocytes, instead of a leukopenia as one might expect in lymphosarcoma. Of interest was the normal serum total protein and serum albumin, which would be against such possible etiologies of hypercalcemia as sarcoid or multiple myeloma. According to the protocol, the patient's total serum proteins subsequently dropped to 4.5 G %; however, some degree of hypoproteinemia would be expected in a person who is not eating.

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Pertinent to the discussion are the elevated serum calcium and low serum phosphorus, and borderline alkaline phosphatase activity. There was no evidence of hyperchloremia or elevated uric acid, which is sometimes seen in primary hyperparathyroidism. The urine showed a fixed specific gravity which is common in hypercalcemia of any etiology, and is secondary to the effects of the elevated serum calcium on the renal tubules, so that they can neither dilute nor concentrate. The x-rays were not helpful in that no cystic or metastatic lesions were seen, as might be expected if metastatic malignancy or myeloma were responsible for hypercalcemia. An x-ray of the skull and spine showed no evidence of osteoporosis; so that on the basis of the x-ray examination, there was no evidence of primary hyperparathyroidism. In this situation, x-rays of the terminal phalanges might have been helpful.

A skin test with purified protein derivative was negative, but might indicate a state of anergy as often seen in lymphosarcoma. Tonsillar biopsy subsequently revealed a reticulum cell sarcoma and as indicated, radiation therapy was begun on the 10th hospital day in view of the known radiosensitivity of such tumors.

The combination of hypercalcemia, hypophosphatemia, and elevated alkaline phosphatase activity with increased urinary calcium persisted, despite the shrinkage in the tonsillar mass. The urinary calcium was somewhat higher than usually seen in primary hyperparathyroidism, and might suggest metastatic disease. In primary hyperparathyroidism, the main effect of parathormone is to increase calcium resorption from bone. Hypercalciuria then results as the blood calcium rises. The urine phosphorus was elevated. This is not specific for a given etiology of hypercalcemia, but again suggests hyperparathyroidism and would result from the known effect of parathormone in decreasing tubular reabsorption of phosphate. The upper limit of normal for plasma parathormone levels in the presence of normal serum calcium level is approximately 4 ule/ml. The reason I stress the point of the normal serum calcium is that the parathormone level can only be interpreted in relation to the serum calcium. In other words, if the serum calcium is high due to any cause other than hyperparathyroidism with normal feedback mechanisms operating, one would expect *decreased* parathyroid secretion. Abnormal regulation of parathyroid secretion is found in primary hyperparathyroidism, and in production of a parathormone-like hormone by another tissue where the primary increase in parathormone levels results in accompanying hypercalcemia, which in view of the autonomous or semiautonomous nature of the lesion, cannot suppress parathormone production. Ectopic parathormone production is seen primarily in neoplasms of the lung and kidney, but tumors in other sites, including the female and male genitourinary tract, and a few cases of reticulum sarcoma, have been reported in this regard.

At this point, an elevated plasma parathormone level in the face of an elevated serum calcium supports a diagnosis of hyperparathyroidism. The etiology of the hyperparathyroidism can only be elucidated further by clinical examination. We have no specific test to identify the site of excess parathormone activity. It can be argued that a calcium suppression test can help establish whether the hyperparathyroidism is due to a parathyroid adenoma, or to parathyroid hyperplasia. Hyperplastic parathyroid glands should not be autonomous, and one should be able to suppress parathormone secretion when a certain serum calcium level is attained, whereas parathyroid adenomas should be completely autonomous. One would also not expect an ectopic tumor which is not under regulatory control to be suppressed. Reports from several groups who have studied the effect of such calcium infusion are not in agreement, and apparently there are hyperplastic glands which do not suppress with infusion of calcium, as well as adenomas that do. The specificity of a decreased tubular reabsorption of phosphate for diagnosing either ectopic or primary hyperparathyroidism is open to question. We have seen a low tubular reabsorption of phosphorus in two-thirds of the patients with hyperparathyroidism. In some cases of sarcoid and myeloma, however, it is also low, and while the presence of a low tubular reabsorption of phosphorus strengthens the diagnosis of hyperparathyroidism, it is not pathognomonic.

This patient subsequently became confused, weak, dehydrated, and febrile, with bilateral infiltrates in both lung fields. Hypercalcemia alone can cause mental confusion. There is no correlation between the level of serum calcium and the degree of the central nervous system dysfunction. The fever could have been due to a number of factors. She could have had pneumonia secondary to aspiration, but most likely it was an infectious process. She was treated with fluids and antibiotics, and the tonsillar mass decreased in size with radiotherapy, but concomitant with dehydration, the BUN rose out of proportion to the creatinine. The urine specific gravity remained 1.010, and the patient became obtunded and slightly edematous. Such edema may have been a result of the lowering of the serum proteins noted. The elevated serum chlorides could be taken as evidence of hyperparathyroidism, since one of the other renal effects of parathormone is a decrease in bicarbonate reabsorption. Patients with hyperparathyroidism also have difficulty excreting an acid load, and tend to have a metabolic acidosis with hyperchloremia, in contrast to other causes of hypercalcemia.

Treatment for hypercalcemia was instituted. One of the simplest ways of treating hypercalcemia is to administer phosphate, which can be given either orally or intravenously. The intravenous form is usually not used except in case of emergency, since it is felt that there is probably greater risk of extraskeletal calcification. The mechanism of action of phosphate in lowering the serum calcium is also open to question. Some groups feel there is sequestration of calcium and phosphate in precipitated form in the soft tissues. Others feel that the effect of increasing phosphate levels decreases bone resorption, and thereby lowers the serum calcium. Most groups give about 100 millimoles a day intravenously over an 8 to 12 hour period, which is the equivalent of about 3 G of phosphorus. Lowering of the serum calcium lasts for three to four days after a single intravenous dose. The same amount of phosphate can be given orally daily, and it is usually quite effective in lowering serum calcium levels within four or five days of therapy. Even with the oral therapy, the safety of prolonged therapy, and the risk of extraskeletal calcification, especially in the kidney, is open to some question.

Sodium sulfate is extremely effective. It acts by increasing urinary calcium excretion, and perhaps also by chelating calcium. Usually 3 L of isotonic sodium sulfate over a nine-hour period will lower the serum calcium for several days. The disadvantage of this particular form of therapy is sodium retention and congestive heart failure. In this patient, one course of sodium sulfate treatment produced a very slight change in serum calcium level.

Recently, some have advocated intravenous Lasix® for the acute control of hypercalcemia, by promoting a calcium diuresis in association with sodium since these two cations share similar tubular mechanisms. The only caution necessary is that because of the severe volume and electrolyte depletion, there will be a compounding of dehydration, so that this will have to be carefully monitored with suitable fluid replacement.

Another form of treatment, and one which I have not mentioned because it would have been contraindicated in this patient in view of coexisting diabetes and edema, is the use of steroids. This is usually effective, however, in etiologies of hypercalcemia not related to parathyroid disease and, therefore, might be expected to be ineffective in cases due to either ectopic production or to primary production of the hormone.

The patient's subsequent course was characterized by some evidence of spread of tumor, as evidenced by the spinal tap which contained abnormal cells, suggesting meningeal involvement.

The patient also had one final complication which appeared to be a hemolytic anemia, which could have been secondary to her disease or perhaps to the medication. No tumor cells were seen in the marrow, and two days before she died she was treated with Decadron®. I can only speculate as to what finally caused her death. Pulmonary emboli were certainly possible, or perhaps she had sarcomatous involvement of the brain stem.

As stated in the protocol, the patient had a reticulum cell sarcoma with hypercalcemia. There was evidence of hyperparathyroidism. Did the patient have two conditions? Namely, did she have a reticulum cell sarcoma and a parathyroid adenoma, or was the production of parathormone related to the ectopic production by the sarcoma? Coexistence of a neoplasm and a parathyroid adenoma has been reported previously. We recently have seen three cases of breast carcinoma with hypercalcemia associated with parathyroid adenoma. As stated above, chemically or by radioimmunoassay, there is no way of distinguishing a case with actopic production of parathormone from one of primary hyperparathyroidism. If one could cannulate the various thyroid veins in a subject, and demonstrate local elevation of parathormone levels, this would point to a parathyroid adenoma. If such levels were lower than that seen in the general circulation in a case with elevated parathormone levels, it would point to ectopic production.

A parathormone-like substance has been extracted from a spleen involved with reticulum cell sarcoma (1). In this case, the parathyroid glands were histologically normal. Therefore, there is precedence for this tumor to produce parathormone, but we have no definite proof that the parathyroid(s) themselves were not hyperfunctioning.

In summary, this was a woman with a reticulum cell sarcoma with hypercalcemia, who could have a reticulum cell sarcoma producing hyperparathyroidism, or an independent parathyroid adenoma and reticulum cell sarcoma.

Dr. Steven Dikman:* Are there any questions?

Question: Could the tumor be secreting a vitamin D-like substance?

Dr. Krieger: I did not mention this because the only tumors that have been shown to produce a vitamin D-like substance which would bring about the hypercalcemia, are carcinomas of the breast.

Dr. Dikman: The surgical biopsy showed a reticulum cell sarcoma characterized by sheets of large pleomorphic cells.

At autopsy, the tonsillar area was fibrotic with no signs of tumor. The mass within the left adnexa proved to be a solid ovarian tumor with a homogeneous appearance and small areas of necrosis (Fig. 1). Microscopic examination showed diffuse infiltration by reticulum cell sarcoma (Fig. 2). The uterus was quite enlarged for a woman of 82 years of age, and contained multiple fibromyomata, but in addition displayed prominent cystic endometrial hyperplasia and endometrial polyps. The right ovary showed cortical stromal hyperplasia and a portion was infiltrated by reticulum cell sarcoma. The tumor also infiltrated the colon and numerous lymph nodes in the periaortic regions, but did not involve other parenchymal organs.

The bones showed osteoporosis and erythroid hyperplasia of the marrow. No tumor could be found within the bone marrow.

In the liver, erythrophagocytosis was noted, correlating with, but not explaining, the clinical finding of hemolytic anemia.

The kidneys were normal except for mild deposition of calcium in and around tubules.

In the lungs a small peripheral, pigmented area with a puckered pleural surface was found. It had a mucoid consistency and proved to be a peripheral adenocarcinoma of the lung (Fig. 3).

Two enlarged parathyroid glands were found. In one, measuring 6 x 3 x 3 cm, a rim of normal tissue was not present. The mass was congested and had a trabecular pattern composed of cells predominantly of chief cell type. No fat

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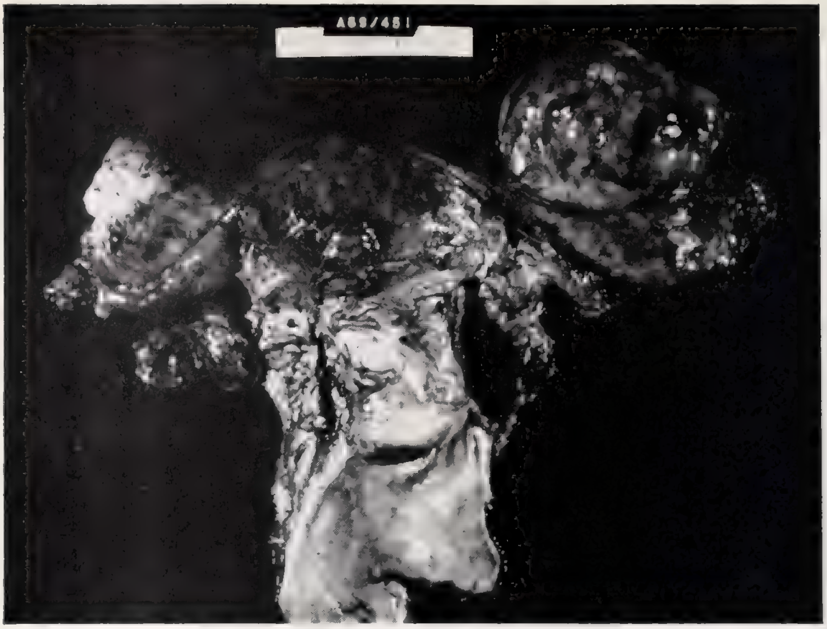

Fig. 1. The right ovarian mass is composed of reticulum cell sarcoma. The left ovary is partially infiltrated by reticulum cell sarcoma. The uterus is enlarged.

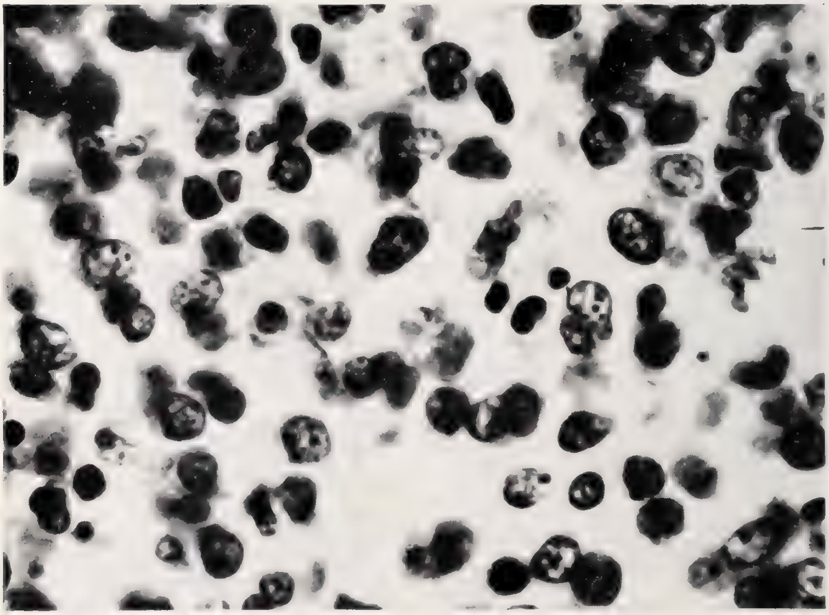

Fig. 2. A field of reticulum cell sarcoma from the right ovary (x 400).

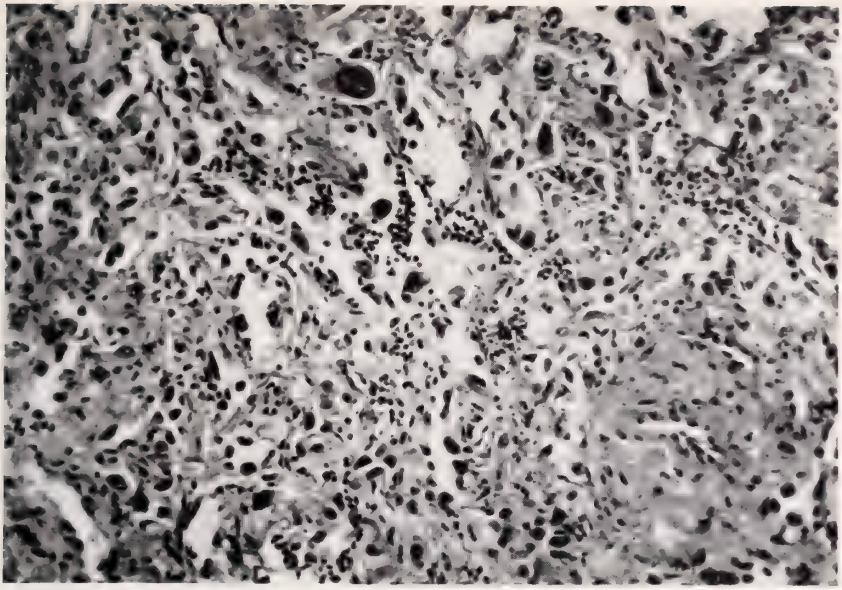

FIG. 3. A peripheral adenocarcinoma of the lung with giant cells (x 400).

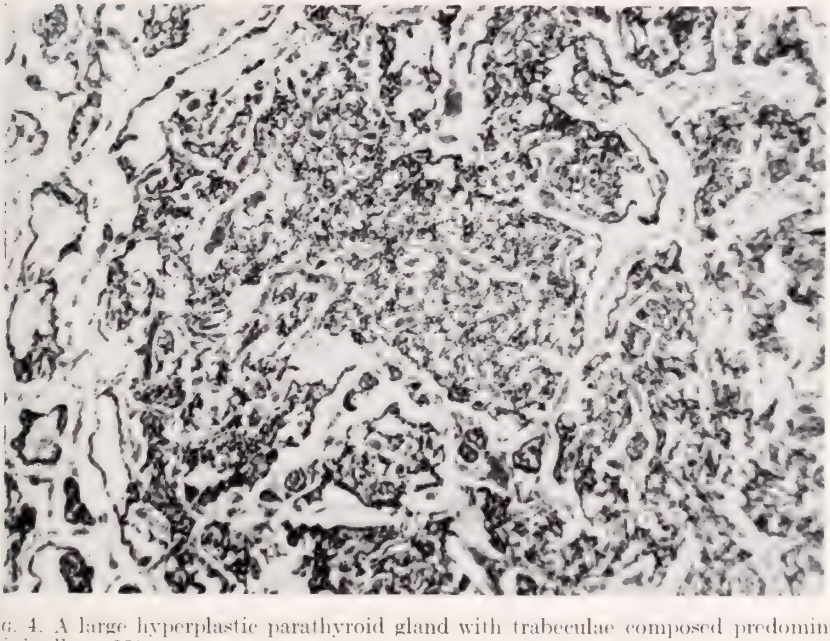

FIG. 4. A large hyperplastic parathyroid gland with trabeculae composed predominantly of chief cells (x 35).

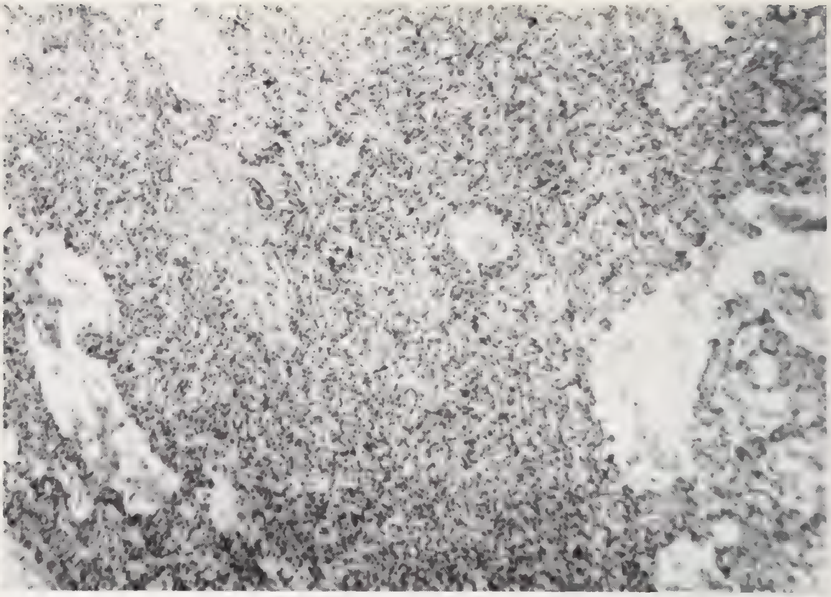

FIG. 5. A hyperplastic parathyroid gland with a small amount of fat. The cells are principally of chief cell type (x 35).

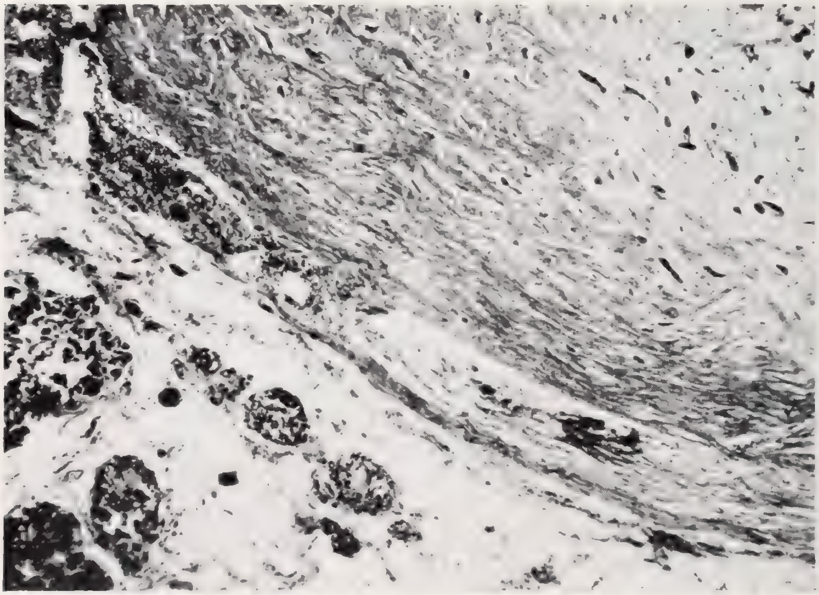

FIG. 6. The border of the sclerosing nonbeta-cell islet cell tumor and atrophic pancreas. Note the small nests of islet cells within hyalinized connective tissue (x 35).

was present within the gland (Fig. 4). The second parathyroid gland was twice the normal size with markedly decreased fat. The parenchymal cords were thickened, and in areas slightly nodular, consisting of chief cells and small foci of oxyphilic cells (Fig. 5).

The pancreas was mildly atrophic, fibrotic, and showed no evidence of calcification. A circumscribed hyalinized nodule containing small nests of cells proved to be a sclerosing nonbeta-cell islet cell tumor (Fig. 6).

Autopsy permission for the brain was not obtained.

Our concepts of the nature of parathyroid tumors have undergone many changes over the years. Originally, most of these tumors were thought to be adenomas. Von Recklinghausen first described the bone changes now associated with hyperparathyroidism, and in 1903 Ashkanazy (and later, others) found that these changes were often associated with parathyroid tumors (2). Albright (3) in 1934 described another type of parathyroid change associated with hyperparathyroidism known as primary clear cell hyperplasia. In 1935 (4) and 1937 (5), Mallory and Castleman attempted to clarify the morphologic characteristics of parathyroid adenomas and hyperplasia, giving some order to a previously confused topic. However, many cases of multiple adenomas were unexplained until 1958, when Dr. Oliver Cope and associates (6) described primary chief cell hyperplasia. In this entity hyperplastic changes of the parathyroid glands are present which are not secondary to a known stimulus such as malabsorption or chronic renal disease. In some areas of the gland, the hyperplasia may become nodular and appear adenomatous. Many of the adenomas previously described both single and multiple, may thus represent a form of nodular hyperplasia (7). As a practical clinical point, removal of one or more of these so-called adenomas without examination and removal of sufficient hyperplastic tissue, may result in recurrence or continuation of hypercalcemia. To complicate the issue, rare cases of coexistent parathyroid hyperplasia, and apparently true adenoma, have been described (8).

Autonomous function may develop in secondary hyperparathyroidism. After initial low or normal serum calcium levels, hypercalcemia may appear with progression of renal disease. This has been called tertiary hyperparathyroidism, and may produce similar histologic changes to that already described (9).

The present case appears to be a form of the multiple endocrine adenomatous syndrome with parathyroid hyperplasia, a nonbeta-cell islet cell tumor of the pancreas and adenomatous goiter. In this syndrome, an unknown stimulus, apparently genetically transmitted, may produce various hyperplastic and nodular changes in multiple endocrine organs, as well as alterations in other tissues (10).

I questioned the family of this patient, and there are two siblings—one aged 65 and the other aged 67—both men who have no referable symptoms due to endocrine dysfunction.

Dr. Krieger: What do you think was the terminal event in the patient?

Dr. Dikman: The patient had bilateral pleural effusions and pulmonary edema. Neither pneumonia nor pulmonary emboli were found.

Final Diagnosis:

1. RETICULUM CELL SARCOMA, MULTIPLE ORGAN INVOLVEMENT.
2. ENDOCRINE ADENOMATOSIS SYNDROME ADENOMATOUS HYPERPLASIA OF THE PARATHYROID GLANDS.
    - a. NONBETA-CELL ISLET CELL TUMOR OF THE PANCREAS.
    - b. ADENOMATOUS GOITER.

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GEORGE JAMES, M.D.
1915–1972

Eulogies Delivered at the Funeral Service of Dr. George James

Everyone in this room, and thousands more around the world, knew George James and, I guess, everyone knew him in a different way.

I knew him as a partner in the incredibly complex business of creating a new and top-drawer medical school where none had existed, and as a cherished and esteemed friend.

While he was many things to many people, he was first and foremost a sympathetic and skilled problem-solver. Our Trustees would confront him with the grave and intricate problems that steadily faced the Board and, at every step along the way, George would advise how the problem could be solved and then he would find the people to solve it. The Faculty, the students, and the medical staff and administration of the Hospital—all of us constantly tapped his wisdom, his patience and his seemingly inexhaustible knowledge of men and medicine. And, with this man at our helm, The Mount Sinai Medical Center came into being, the great Annenberg Building rose high above our campus, and Mount Sinai School of Medicine attracted a large and distinguished Faculty, became affiliated with The City University of New York, and opened its doors to young medical students from all over the nation.

From the beginning, George James blended thoroughly with Mount Sinai and its traditions of the past and its hopes for the future. Explaining why he had cast his lot with ours, he said, "I think probably the best time to be a Dean is before a medical school exists. In an established school, the curriculum is set, the school frozen in tradition—you have to wait years to make changes. But here, we are building, and we can build as we want for the highest possible standards."

The legend that has grown up around Mount Sinai—that it has always been able to find the men and women it needed when it needed them—was never more effectively supported than when we chose George James to lead us through the Institution's period of greatest change and expansion.

I had the good fortune to serve on the search committee that chose George James to be our first Dean and President of our great Center. I know I can speak for all the members of that committee in saying that we never, ever, regretted our choice. No one could have so successfully organized and structured a fledgling institution so that in a very few years it is regarded as one of the great and most sought after medical schools in our nation.

In selecting George James to serve us, Mount Sinai had excellent company. His nation chose him to preside over the President's Task Force on Health and the National Health Council and to represent it in the World Health Organization. His State chose him to serve as President of the New York State Academy of Preventive Medicine, as President of the New York State Epidemiological Society, and as Consultant to the Legislature on Health matters. And his City chose him as President of the Associated Medical Schools of Greater New York, as Chairman of its Health Research Council, and as its Commissioner of Health.

George put his beliefs into practice constantly. As Commissioner of Health, he was responsible for fluoridation of the City's water supply and for the establishment of family planning services and for launching a program that affiliated the City's neighborhood health centers with outpatient departments of teaching hospitals. Two weeks after he was sworn in, he opened the Bedford Pediatric Center, designed to treat any sick child. This walk-in clinic was the first such comprehensive service offered by any health department in the nation. The citation accompanying the Bronfman Prize of the American Public Health Association called George James "a dynamic force in bringing public health to its full potential."

In this sorrowful moment, we all want to know again this wonderful man, even if briefly. I am sure each of us knew him differently. I knew him as a close friend, a great and trusted leader, and a person to whom I could bare my innermost thoughts without restraint.

Speaking for myself and for the Trustees of our Center, our School, and our Hospital, all of us will miss him tremendously, but we are all enriched by our experiences with him these past too-few years.

GUSTAVE LEVY
Chairman of the Board,
The Mount Sinai Medical Center

Emotion is an impediment to a thoughtful evaluation of a man who meant so much to so many people and to so many institutions. At Mount Sinai George James, as Dean and President of the Medical Center, was a force shaping the philosophy of a budding medical school based on the tradition of a prestigious hospital, which had always been innovative but inward-looking, and which, under his leadership, acquired a new dimension. Mount Sinai was changed by the stewardship of this man who was dedicated to maintaining the Hospital's excellence, but supplementing it by considering the health problems of the community around him in the city, in the nation at large, and, indeed, of the entire world. A revolution in the thinking of society (and of government as its arm) regarding health care was predicted by him years before the world health crisis became a cliche. By seeing problems in public health, health care delivery and environment long before they became a subject for common thinking, he was in the forefront of those offering constructive solutions to diseases before they became rampant. By being an advocate of preventive medicine, he applied this viewpoint to the health problems of society. George James was responsible for Sinai's changed image and leadership in community medicine in the 70s This great achievement enabled him to maintain the required balance between classical medicine and the new health science of today demanded by the nation He was rewarded for this achievement and for his leadership in leading and organizing the school by the affection and respect of the faculty, of the students, and of the entire Sinai family.

What George James did as a man could only be accomplished by his fortunate combination of personal attributes—patience to listen and a rare intelligence, bordering on genius but masked by a quiet and simple appearance, combined with a concealed drive, ambition and integrity. The man, who had almost finished an authoritative book on the health crisis of the cities, had progressed through a series of responsible jobs in public health in several states and in New York City. He was an advisor and official of many different governmental agencies, of foundations, of voluntary health agencies, and of medical societies and their councils.

The nation loses in him one of the powerful forces shaping the health policies of America. It will be almost impossible to replace him, not only in Mount Sinai, but also in the nation at large.

The work he accomplished at Mount Sinai in an all too brief span of time will live on for many years to come. We can be grateful for this and take comfort from it.

It is hardly possible in a few words to describe what Sinai and the country have lost, but it should be added that some of us, and surely I, have lost a friend with whom one did not have to always agree to admire his wisdom, his clarity of thought, his decency and fairness. We who enjoyed his friendship share with his wife and daughter a personal loss difficult to put into words.

HANS POPPER, M.D., PH.D.
Acting Dean, Mount Sinai School of Medicine
Acting President, The Mount Sinai Medical Center
and
Heinz Given Professor, and Chairman
Department of Pathology
Mount Sinai School of Medicine

In Memoriam

KERMIT E. OSSERMAN, M.D.

1909–1972

Only a few months ago there appeared in this Journal a remarkable tribute to Dr. Kermit E. Osserman—a whole issue devoted to myasthenia gravis as reflected in the work carried on at The Mount Sinai Hospital by a group of physicians and surgeons of which he was the unquestioned inspiration and leader. Now Kermit is gone, the victim of a massive myocardial infarction suffered on January 22, 1972. His untimely demise, at the age of 62 and at the height of his powers, came as a deep shock. I hope I can convey the poignancy of this sad event, and the rarity of the qualities that marked him as a man, a physician, and an investigator.

Kermit was a native New Yorker, born on June 21, 1909. He received his primary and secondary education in local schools, his A.B. degree at Johns Hopkins University in 1929, and M.D. degree at the University of Maryland Medical School in 1933. Returning to New York, he served his internship at the Bronx Hospital. This completed, in 1935 Kermit began two enduring associations, his marriage to Dorothy R. Jacobs, whom he had met in Baltimore, and who was thenceforth to be his inseparable companion and closest aid, and his membership on the staff of The Mount Sinai Hospital. Dr. Samuel Peck, a lifelong friend, stimulated his interest in dermatology, and Kermit initiated his professional career in 1935 as Clinical Assistant in Dermatology at The Mount Sinai Hospital, and Adjunct Physician, Dermatology, at the Bronx Hospital. Obstetrics and Gynecology then beckoned, and from 1940 to 1944 he served as Senior Clinical Assistant in Gynecology at The Mount Sinai Hospital. But he still had not found himself, and in 1944 he consulted Dr. George Baehr about turning to internal medicine. Thus it came about that in 1944, nine years after completing his internship, Kermit began a two-year term as Resident in Medicine. There followed a fruitful period of work in diabetes, serving in the Diabetes Clinic as Senior Clinical Assistant, Medicine, and Research Assistant in Medicine. Several solid publications on diabetes appeared, also a notable paper, with Dr. Max Ellenberg, the first to recognize the role of shock in the genesis of central liver cell necrosis. Productively engaged, and with a thriving practice, Kermit seemed now firmly ensconced as a specialist in diabetes.

Then, in 1950–51, Kermit encountered in his practice a case or two of myasthenia gravis, and he was both fascinated by the problems of causation and challenged by the problems of management. At the time there was no special facility for the study and care of this dread disease at The Mount Sinai Hospital, nor indeed in all of the New York area. Kermit decided to create one. In 1951 he came to see me (then Director of the Department of Medicine) about starting a Myasthenia Gravis Clinic. I was delighted by his

KERMIT E. OSSERMAN, M.D.
1909–1972

initiative but appalled by the magnitude of the venture. This was a disease of repetitive crises that could drain the energy, time, and emotional resources of any physician even if not otherwise employed, and Kermit was already overburdened. Research on pathogenesis was then almost exclusively neuro-physiological, in which he had no training. Such hesistancies were overcome, however, by his enthusiasm and determination. Kermit organized a Myasthenia Gravis Clinic in 1951, gathered together a small but dedicated group of professional associates, pressed into service his wife and daughter (Ruth Sue), and found modest laboratory space, personnel, and financial support for research. Patients afflicted with myasthenia gravis flocked to the new clinic in unexpected numbers, because they soon learned that they were to receive intensive and sustained personal attention; many, in fact, volunteered to become an integral part of the research team effort. By 1958 the Myasthenia Gravis Clinic, under Kermit's aegis, could draw upon an experience with 350 cases, all meticulously documented in a standard text (Osserman, K. E., *Myasthenia Gravis,* New York, Grune & Stratton, 1958, pp. 1–286). By 1971, the number had grown to over 1200, who came from far and wide (Osserman, K. E. and Genkins, G.: Studies in Myasthenia Gravis: A Review of a Twenty-Year Experience in Over 1200 Patients, Mount Sinai J Med 38:497–537, 1971).

In the intervening 20 years, progress has been slow and often painful, interspersed with many disappointments and harrowing experiences. The cause has not been established and no certain cure has been found, nevertheless, the lot of the patient afflicted with myasthenia gravis has steadily and markedly improved. The contributions made by Kermit and his associates to these therapeutic advances have been substantial. In 1952 Osserman and Kaplan introduced the edrophonium test as an aid in the diagnosis of myasthenia gravis, in 1953 as an aid in management, notably in the vital and sometimes difficult distinction between myasthenic and cholinergic crisis. The usefulness of the test was soon confirmed, and it is now universally practiced. As new anticholinesterases (pyridostigmine, octamethyl pyrophosphoramide, ambenonium, germine) were successively made available, they were subjected to rigorous clinical trial. The use of large doses of ACTH, in earlier trials thought to be too hazardous, was resurrected, and found to be beneficial when untoward reactions were adequately controlled by respiratory support and anticipatory tracheostomy. Thymectomy, too, despite many discouragements, was given a protracted trial until finally, with improved surgical and auxiliary techniques, it could be demonstrated that the response, while delayed, was often unequivocal. These were all large-scale, long-term clinical studies, conducted with attention to detail; and they carried conviction. What does not appear in these reports is the ceaseless vigilance that was required in the care of the desperately ill Group III and Group IV patients, and the unremitting demands on physician and nurse. Only the most dedicated would undertake such a mission; the striking successes were hard earned.

In the meantime, Kermit and his collaborators were busily engaged in laboratory investigation of the underlying causes of myasthenia gravis. Almost from the start, and before the role of the thymus in immune disorders was appreciated, he sensed the immunologic implications of the disease. As early as 1956, Nastuk, Osserman, and Plescia showed a decline in serum complement, roughly inversely proportional in degree to the severity of disease. In 1960, with Strauss and others, circulating antibodies which reacted specifically with striated muscle were detected in the serum of many patients with myasthenia gravis. This observation has stimulated continuing investigation in a number of laboratories. Its pathogenetic significance is not clear, but it has been suggested that the antibodies, acting in concert with sensitized lymphocytes, may somehow produce immune changes leading to defective neuromuscular transmission. In any event, the association of the thymus with myasthenia gravis has taken on increased significance in recent years, and thymectomy has been provided with a more than empirical rationale. These interesting developments were recently reviewed by Kermit's associates, Drs. Rule and Kornfeld (Rule, A. H. and Kornfeld, P.: Studies in Myasthenia Gravis: Biologic Aspects, Mount Sinai J Med 38:538–572, 1971).

Kermit authored or coauthored more than 100 papers, he wrote the standard textbook on myasthenia gravis previously mentioned (a second edition was in preparation), and he contributed chapters on myasthenia gravis in a number of collective volumes. A relevant bibliography will be found in the articles already cited here, and at the end of Dr. Berson's commemorative remarks (Berson, S. A.: Contributions of The Mount Sinai Hospital to the Study and Care of Patients with Myasthenia Gravis, Mount Sinai J Med 38:602–608, 1971).

Recognition was not long in coming. As an accepted leader in his chosen field, Kermit was invited to serve as chairman of the Second International Symposium on Myasthenia Gravis held in Los Angeles in 1959, and again in 1965 at the Third International Symposium in New York (Ann NY Acad Sci 135:1–680, 1966), and once more in 1970 at the Fourth International Symposium. He was a founder and member of the Medical Advisory Board of the Myasthenia Gravis Foundation from 1952, and its chairman 1959–61. He served on national committees for the evaluation of drugs used in myasthenia gravis, notably for the U. S. Public Health Serivce. He was invited to lectureships in many parts of the world, and on several occasions his lucid exhibits at conventions of the American Medical Association won prizes. At Mount Sinai, Kermit rose steadily through the ranks to appointment in 1970 as Clinical Professor of Medicine at the School and Attending Physician at the Hospital. But his greatest reward, and the one that gave him most satisfaction, was the reduced mortality and morbidity of his patients. It is not given to many physicians to take on so desperate a disease and to accomplish so much in ameliorating its course.

It is evident from Kermit's career that he was an extraordinarily energetic, determined, and courageous man. To all who knew him personally he was also an innately modest man, without pretensions; and success did not spoil him. To his patients he extended inexhaustible sympathy and help. To his professional associates he brought an infectious and inspiring enthusiasm. He was completely involved in whatever he undertook. How well I remember his bubbling reports of successes when he came to report a triumph, and how he sank into a chair in utter despair when some treatment or experiment failed.

This was a rare spirit. We all share with Dorothy and Ruth Sue a sense of bereavement, and proffer our deepest sympathy and the consolation of Kermit's great achievement.

ALEXANDER B. GUTMAN, M.D.
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Nonspecific Stenosing Arteritis of the Aorta and Its Branches: A Study of a Possible Etiology

P. K. SEN*, M.D., Ph.D., S. G. KINARE, M.D., M. D. KELKAR, M.D., and
S. A. NANIVAD-KAR, M.D.

Professor P. K. Sen, recently a visiting Professor at the Mount Sinai School of Medicine and a distinguished teacher and investigator in his native India, presents in a multidiscipline approach the provocative thesis that in the exhaustive series of eighty cases of nonspecific arteritis observed by him, tuberculosis may be etiologically linked to the disease process. [*Editor's note*]

Introduction

Nonspecific aortitis is an inflammatory condition of the aorta of an unknown nature which involves the main vessel and often the mouths of main branches such as the subclavian, carotid, celiac axes, and the renal arteries. The end result is usually a coarctate constriction or occlusion of the lumen and, occasionally, aneurysm. Depending on the extent, segment, and branch of the aorta involved, ischemic changes are produced in the brain, upper extremities, gastrointestinal tract, kidneys, or lower extremities. These manifest themselves clinically as giddiness, visual disturbances, cataracts, claudicatory pains in the arms and legs, abdominal angina, headache, edema, convulsions, and unconsciousness. The symptoms of each patient, depend on the distribution and extent of the disease.

This condition is a fairly common clinical entity at the King Edward Memorial Hospital in Bombay, where we have documented eighty cases. However, until about ten years ago, this was thought to be a rare condition, in our hospital and in the entire Indian subcontinent, where only sporadic case reports had appeared (1, 2).

We recognized our first case in 1954, and our interest in this condition was aroused in 1960 when we saw three more cases in quick succession. We reported clinical and histopathologic studies in all four cases in 1962 (3). At about the same time Konar et al (4) and Basu et al (5) also reported similar findings from another center in India.

The earliest mention of this disease in literature is from Great Britain, Savory's report of a case in 1854 (15). There are now well over a hundred reports, mainly from Japan, Scandinavia, the United Kingdom, other European countries, and the United States (6–13). In 1908 Takayasu (14) aroused the attention of the Japanese medical world by presenting at an ophthalmology conference the case history of a young woman whose ocular fundus showed a peculiar capillary flush and who had absent pulses in the arms. Professor Onishi, who was present at the conference, narrated the case histories of other patients with similar findings which he had seen.

From the Departments of Surgery and Pathology, Seth G.S.M. College & K. E. M. Hospital, Bombay, India.

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The clinical picture as presented in these reports from various countries has differed to a considerable extent. The Japanese, for example, emphasize "pulseless disease" due to a marked predilection for involvement of all branches of the aortic arch with resultant severe cerebrovascular insufficiency, cataracts, and blindness. Involvement of the aortic bifurcation, or marked narrowing of the abdominal aorta giving rise to poor or absent pulsations in the legs, is uncommon in their cases (16). Reports from the Scandinavian countries emphasize the occurrence of occlusion of the branches of the aortic arch, constriction of the thoraco-abdominal aorta, and frequent involvement of the pulmonary artery (8, 17). Cases of subisthmic aortic stenosis with "acquired-coarctation-like syndrome" have been occasionally reported in the American literature (18, 19). South African (20) and Malaysian cases (21) have occlusion of a vessel of the aortic arch, narrowing of the thoraco-abdominal aorta, and frequent involvement of the left subclavian and renal arteries. These patients have severe hypertension, weak pulsations in the legs, and absent pulse in one arm. Our own cases are frequently of this type (Figs. 1–4).

The disease has been called by various names, some eponymous, some descriptive. Examples are Takayasu's disease, young female arteritis, aortic arch syndrome, Reversed coarctation, stenosing aortitis, Raeder-Harbitz syndrome, pulseless disease, Martorell's or arch syndrome, and middle aortic syndrome. Strachan (22) lists 15 synonyms, and we have uncovered 17 more.

Until the middle 1960's it was mistakenly believed that these were different disease entities. However, there was an outstanding common denominator in all the reports of a marked predilection of the disease in young females. The ratio of females to males was anywhere from 3:1, as in our material, to 9:1 in the Japanese and Scandinavian cases. Furthermore, histologic examination of all cases showed a nearly identical and constant picture—the adventitia was markedly infiltrated with collagenous material. The vasa vasora showed endarteritis and perivasal small mononuclear cuffing. Plasma cells were scarce or absent, a very strong indication (apart from repeatedly negative serology) that the lesion was nonsyphilitic. Later, the vasa vasora showed obliterative changes and dense fibrosis (Fig. 5). Variable amounts of destruction of media and elastica were seen (6). Mild lesions exhibited focal damage, but in some cases almost total destruction was produced with formation of aneurysms. Productive granulomatous lesions with large collections of lymphocytes and occasional giant cells were sometimes encountered. Generally, however, the cellular reaction was moderate or scanty (Fig. 7). The disease mostly affected the intima with severe proliferative fibrosis, some secondary atheromatous changes, occasional calcification in advanced cases, and thrombosis. Thickening of the intima occurred early and led to narrowing of the lumen.

In summary, it may be said that the disease is essentially a panarteritis affecting all coats with adventitia showing the earliest changes.

The infiltrative cellular pattern of this disease is nonspecific (Fig. 8), yet histologically characteristic. The pathologic picture is highly suggestive of an immune mechanism playing a role but the nature or the mode of action of the antigen has never been made clear. Ask-Upmark (8, 23) surveyed the literature

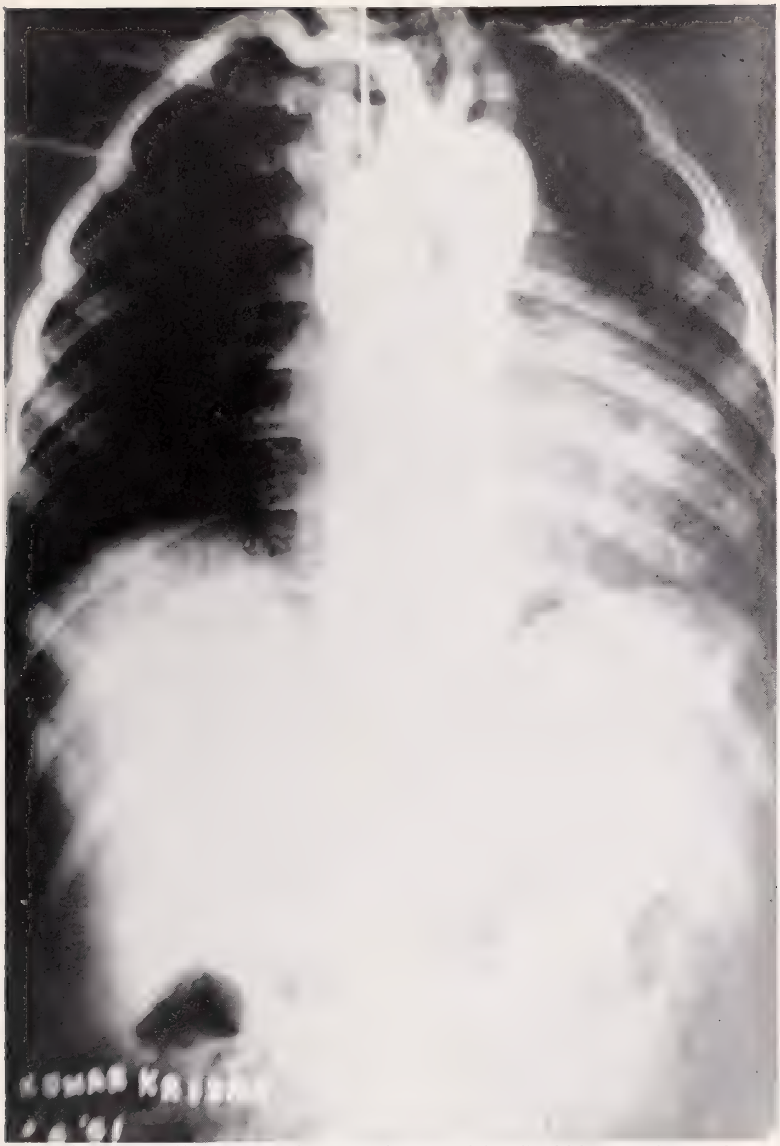

FIG. 1. Typical supradiaphragmatic stenosing aortitis—"Middle aortic syndrome." Note occlusion of left subclavian artery.

of cases outside Japan and suggested that the disease was common in countries such as the United Kingdom and Scandinavia, where the incidence of rheumatic fever is high. In his own series, history of rheumatic fever was given by 95 percent of patients. Japanese workers (16, 6) feel that the history of these patients is strongly suggestive of a collagen disorder.

Patients and Methods

Our experience has been unusual and different. In our first four cases, we found associated tuberculous lesions in all. In three autopsied patients tubercu-

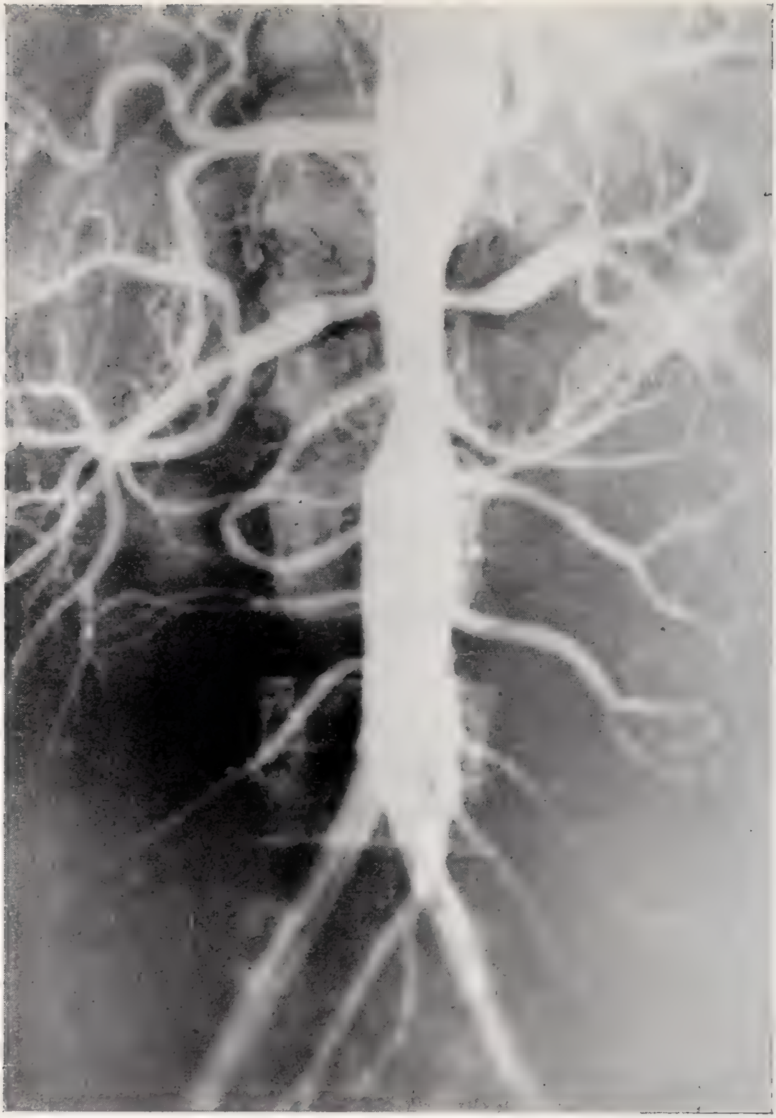

FIG. 2. Intradiaophragmatic "renal variant" of stenosing aortitis.

losis affected the liver and in the two kidneys. The retroperitoneum was not dissected. In the fourth patient, a biopsy of cervical lymph node revealed tuberculosis.

From 1960 till 1966, we saw another thirty cases. In eleven, a definite tuberculous focus was demonstrated histologically either by autopsy, biopsy, or clinical examination with x-ray of the chest, thus bringing the incidence of tuberculosis to 15 in 34 patients. Even though the incidence of tuberculosis in India is high, it is seen in only about ten percent of necropsies in a general hospital such as ours with a necropsy rate currently around 3,000 a year. Such a high incidence of tuberculosis in these cases could not be dismissed casually as

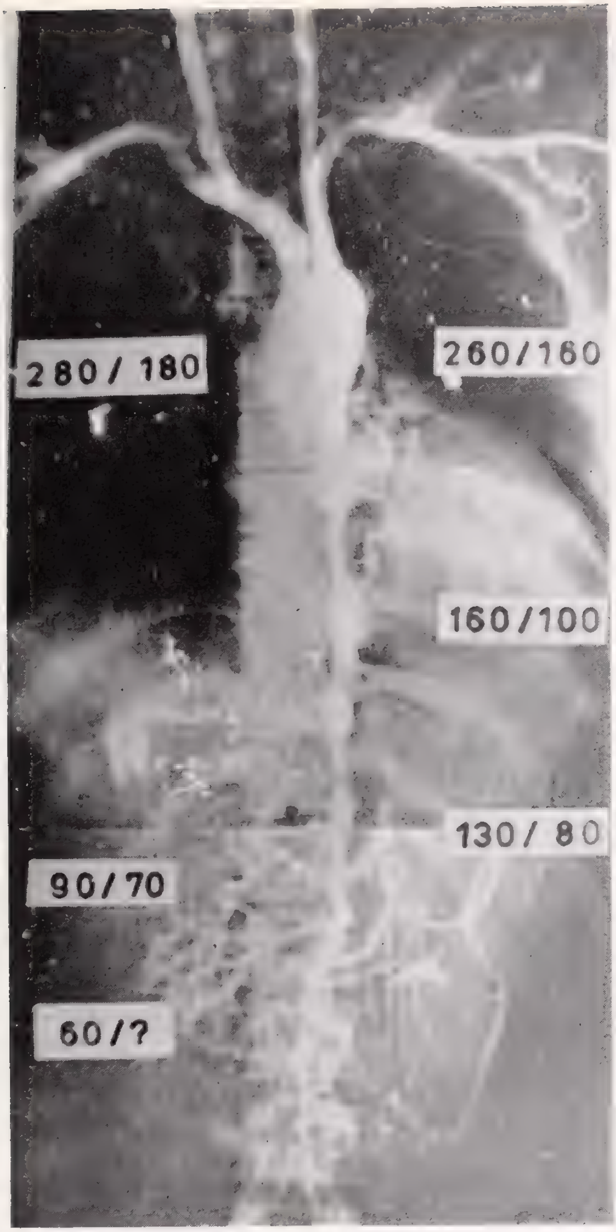

FIG. 3. Multiple supra- and intradiaphragmatic stenosing lesions—"rosary type"—with a succession of pressure gradients and post stenotic dilatations.

merely fortuitous. Another significant fact noticed in necropsies was the frequent tuberculous involvement of paraaortic lymph nodes adjacent to the diseased aortic segment (Figs. 9, 10). Biopsies of such nodes at operation revealed tuberculous inflammation in over half.

We next attempted to demonstrate tuberculosis in retroperitoneal nodes by lymphangiography, which we performed for the first time in a patient of such

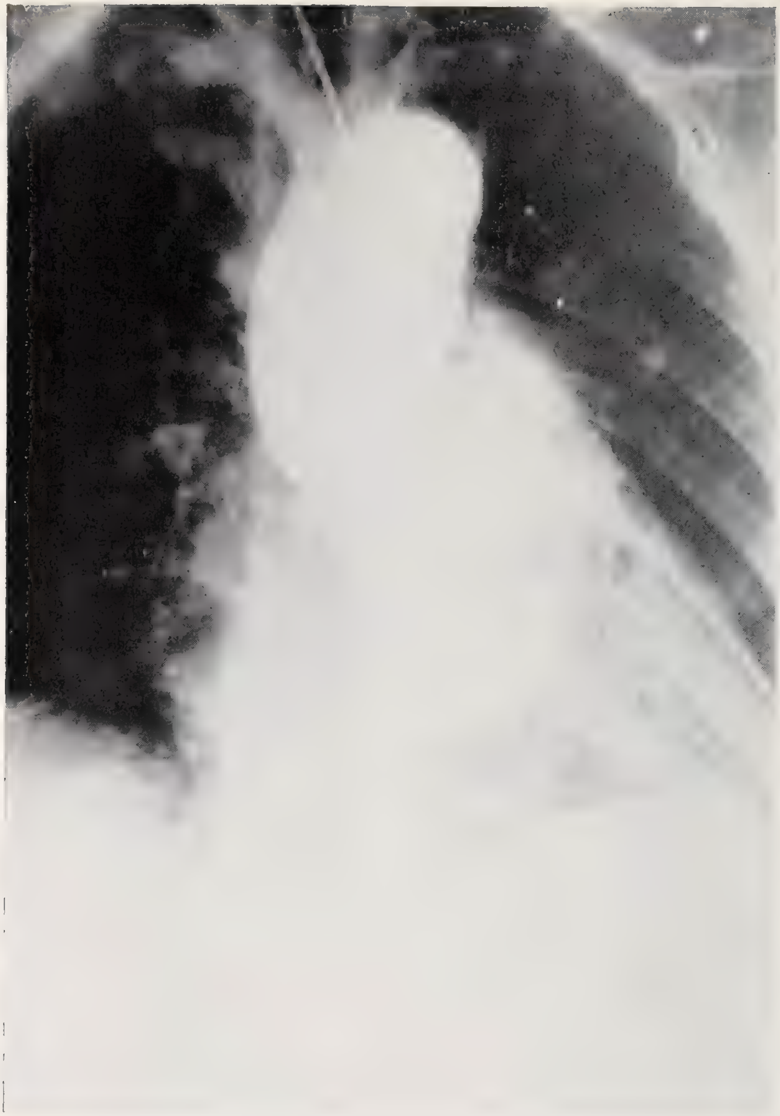

FIG. 4. Aneurysmal variant of stenosing aortitis.

aortitis in June 1966. In this patient, as well as a subsequent three, the lymph nodes were distorted, destroyed with "cut-outs," or efferent channels were completely blocked around the site of vascular pathology (Fig. 11).

We put forward the theory (24, 25) that nonspecific aortitis (at least, in our location) may be caused by an immune reaction produced by the seeding of tuberculous antigen in the aortic wall from a focus somewhere else in the sensitized individual, particularly in the paraaortic lymph nodes. Our premise had strong support in the histology of the disease of the aorta as compared with that seen in tuberculous meningitis (Fig. 12) (26). As Doniach (27) showed in tuberculosis, inflammation primarily involves vessels, and probably initially

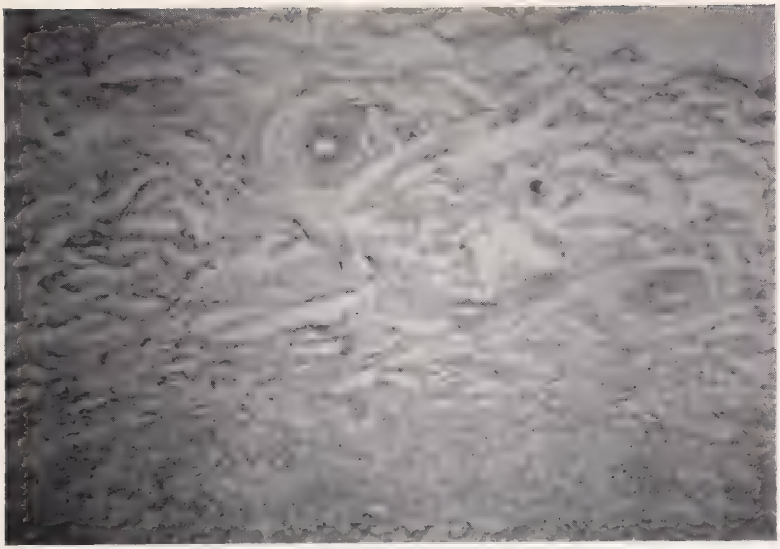

FIG. 5. Collagenous infiltration of the adventitia with marked thickening of vasa vasora.

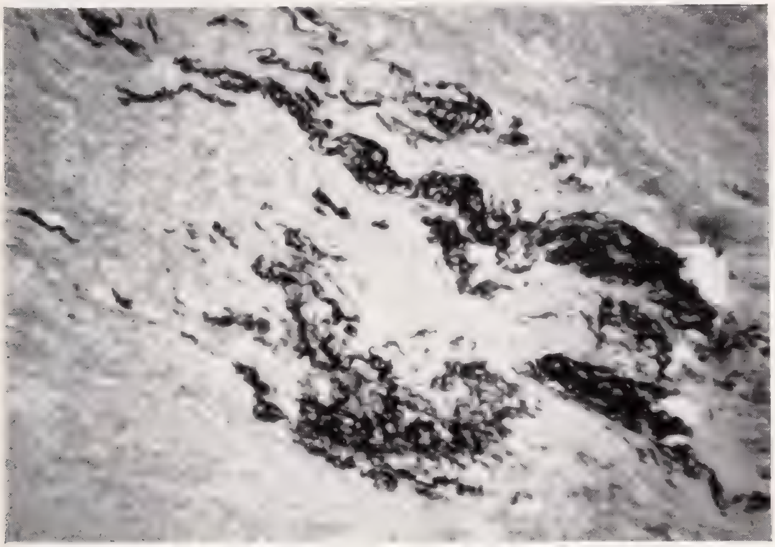

FIG. 6. Section from an aneurysmal lesion showing extensive destruction of elastica.

affects the adventitial vasa vasora. Tubercles are difficult to demonstrate in a vessel wall. The essential vascular response is marked fibrous intimal proliferation, and this is also seen in the vasa vasora. In aortic disease it affects the intima of vasa vasora as well as the intima of the aorta itself. The medial lesions appear to be secondary to changes in the vasa vasora, and the medial granulomatous lesions most probably represent a reaction to degenerate and fragmenting elastica.

We have performed a number of studies, particularly with rabbits, to reproduce this disease experimentally. The rabbit has a small blood volume, and does

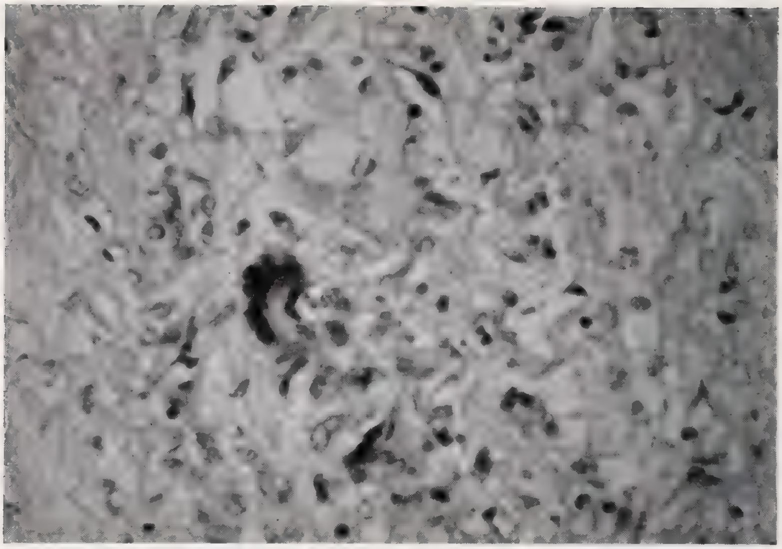

FIG. 7. Focal granulomatous lesion with a giant cell in the media.

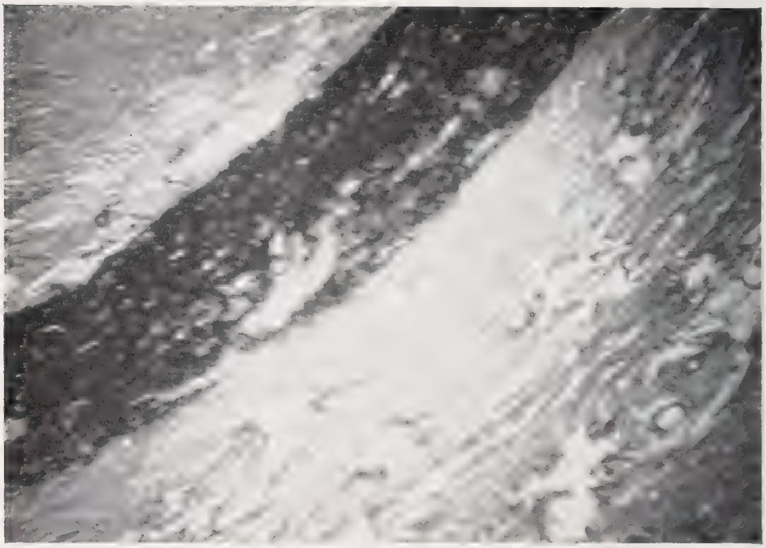

FIG. 8. Section from the diseased segment of the aorta showing changes in all 3 coats, as described.

not tolerate much blood loss or the shock of peritoneal injury. Splitting through the gap between sacrospinalis and internal oblique muscles gave a direct approach to the rabbits lumbar aorta without opening the peritoneum (Fig. 13). Induction anesthesia was best achieved with 25 mg Thiopentone® kg body weight, given intraperitoneally and anesthesia was maintained with a swab dipped in ether held near the nose. Clinical cases wherein periadventitial thickening and reaction in the vasa vasorum far exceeded changes in the intima indicated that the disease process might start as periaortic inflammation with

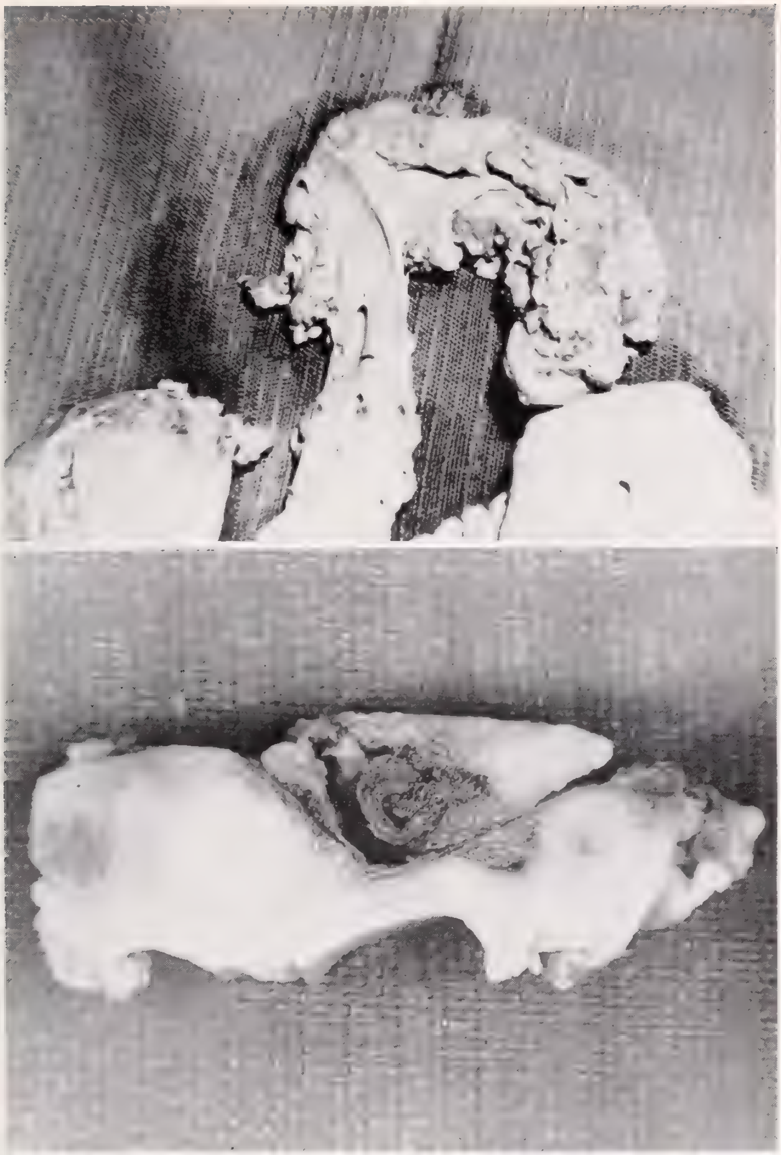

Fig. 9 and 10. Postmortem specimens showing extensive periadventitial thickening. The inferior vena cava and aorta are buried in a mass of caseous lymph nodes.

intimal proliferation following in response to adventitial inflammation. Medial destruction could then occur at a later stage when obliterative changes in the vasa vasora took place. Therefore, it was decided to inflict injury in periaortic tissue rather than in the aortic wall. Accordingly, we took groups of rabbits and subjected the aorta to several kinds of injury.

Surgery. After injection the rabbit was placed in a right lateral kidney position with a pad under the dorso-lumbar region. A rectangular part of the body extending from the tip of the eleventh rib to the iliac crest and the lateral

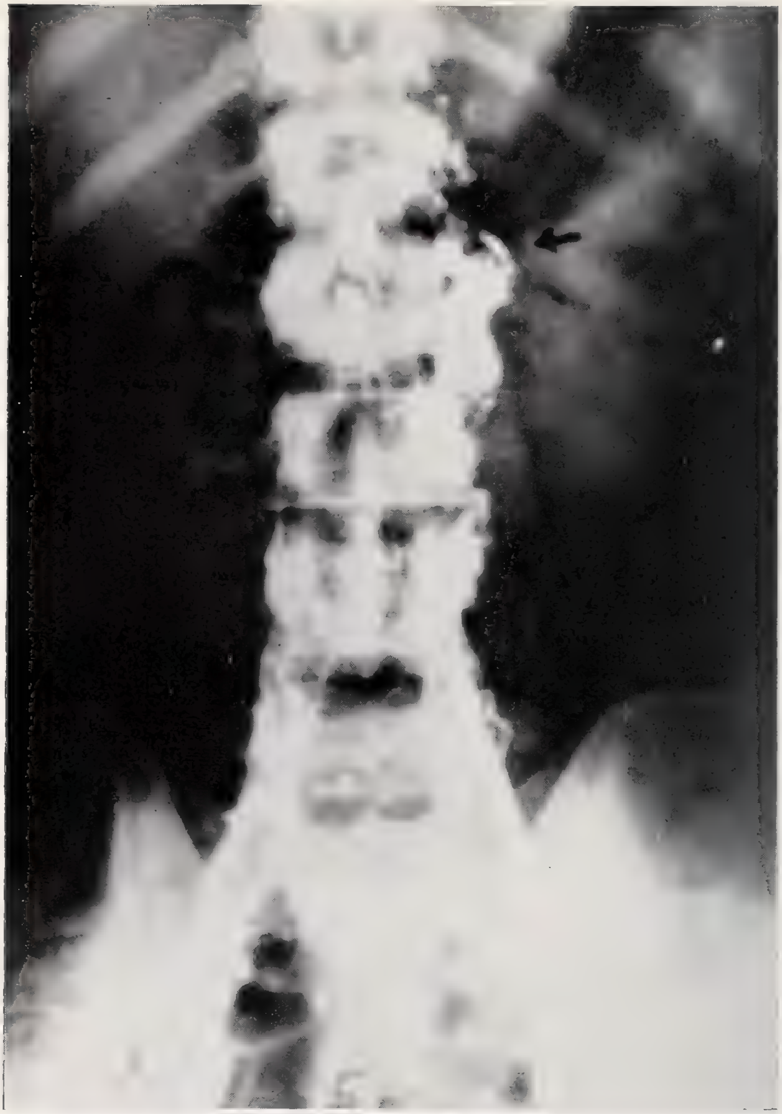

FIG. 11. Lymphangiogram showing the paraaortic lymph nodes which are destroyed by tuberculous caseation adjacent to the diseased segment of the aorta.

edge of the vertebral column to the midline of the abdomen was shaved. A skin incision was made from the tip of the eleventh rib obliquely downward and forward for two inches. A plane of cleavage was developed between the lateral margin of the sacrospinalis and internal oblique muscles. Blunt dissection was used to reflect the peritoneum anteriorly without injuring it and expose the aorta (Fig. 13). For periaortic injection a BCG syringe and 23-gauge needle was used. The mode of injuries inflicted were as follows:

Mechanical. The adventitia over a segment of abdominal aorta between the renal arteries and bifurcation was stripped.

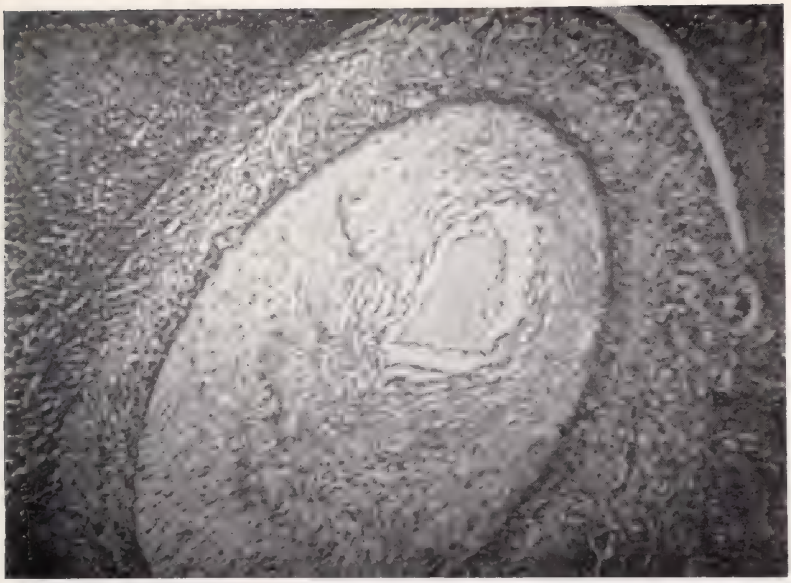

Fig. 12. Typical changes in the wall of a small artery bathed by tuberculous material in a case of tubercular meningitis.

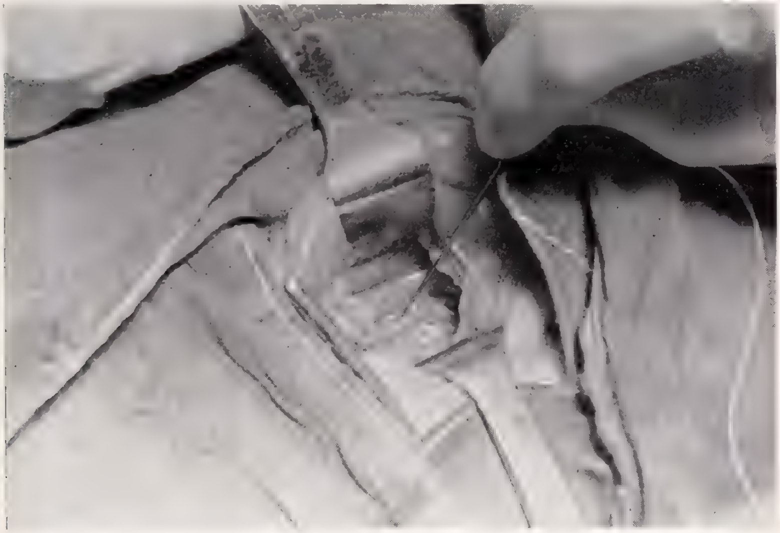

Fig. 13. Exposure of the rabbit aorta by a muscle-splitting extraperitoneal approach.

Bacteriologic

A. *Proteins*

1.) *Horse serum:* One ml of material obtained from Haffkine Institute, Bombay.
2.) *Old tuberculin:* One ml of evaporated glycerol medium in which Mycobacteria had been grown and then removed by filtration.

3.) *P.P.D. (Purified protein derivative)*: One ml of a standard preparation of tuberculin containing specific protein isolated by ultra filtration and repeated trichloracetic acid precipitation of culture filtrates of Mycobacterium tuberculosis.

4.) *Freund's adjuvant:* One ml of Freund's adjuvant containing killed acid fast bacilli.

B. *Live organisms*

1.) *Streptococcus hemolyticus:* Four-tenths ml of a cultured pathogenic strain.

2.) *B.C.G.:* One ml of a suspension of bovine living tubercle bacilli previously attenuated by prolonged subcultures in glycerine-bile potato medium.

3.) *Bovine tubercle bacilli:* Eight-tenths ml of a cultured pathogenic strain obtained from Haffkine Institute.

Chemical injury

A. *Hypertonic saline:* 0.5 ml, 25% NaCl.

B. *One-fourth percent zinc chloride:* 0.5 ml, 0.25% ZnCl.

C. *Phenol in glycerine:* 0.5 ml, 2.5% phenol in glycerol.

D. *Phenol, glacial acetic acid, and glycerine:* 0.5 ml Prosting solution.

E. *Multiple injections:* After injecting 0.5 ml of the chemical, a fine polyethylene catheter was placed by the side of the aorta and fixed by a stay suture in the para vertebral muscles. It was brought out of the abdomen through a stab incision and its lumen kept sealed. Through the catheter 0.5 ml of the sclerosing chemical was injected every week over a period of 4 weeks.

Control experiments: One ml, 0.9% NaCl.

Experimental Results

Immediate postmortem aortograms done in 29 experimental animals were carefully compared with those of two controls (Fig. 14a, 14b). A demonstrable lesion, such as constriction of the lumen, was noted in 8, and was reconfirmed at autopsy (Figs. 15a, 15b, 16, 17). These were one each from the horse serum, B.C.G., and the human Mycobacterium groups and 5 from the bovine series.

After sacrificing the rabbits, the entire aorta from the ascending limb to the bifurcation, including the common iliac arteries, was dissected and fixed in formalin. Sections were cut and stained with hematoxylin and eosin, an elastic stain, and Van Gieson's method; the periodic acid—Schiff technique, and with Alcian blue.

1.) *Horse Serum:* Three rabbits sacrificed after 2–10 months showed a few areas of giant cell reaction in the periadventitial tissues. There was slight thickening of the adventitia, and occasional focal destruction of the elastica. The intima showed proliferation. The changes, however, were not remarkable.

2.) *Old Tuberculin:* No change was noticed in any of the rabbits.

3.) *P.P.D.:* No change was noted.

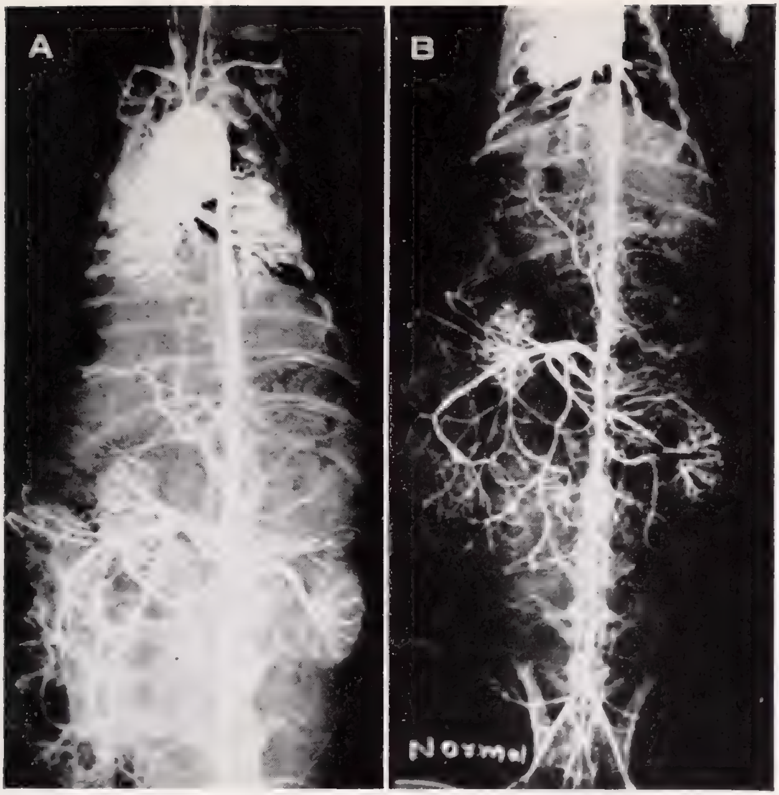

FIG. 14a. and b. Aortograms in two normal rabbits.

4.) *Freund's adjuvant:* Only one of the 10 rabbits showed slight thickening of the adventitia and intima.
5.) *Streptococcus hemolyticus:* No change was noted.
6.) *B.C.G.:* Two of three rabbits which died after 8 weeks showed extensive granulomatous reaction around the aorta with mononuclear cells, plasma cells, macrophages, giant cells, and fibrous reaction. There was slight intimal thickening. One of the rabbits sacrificed after 3 months showed similar changes.
7.) *Bovine tubercle bacilli:* In rabbits sacrificed after 8–12 weeks, three showed a mass of tuberculous granulation tissue in the periaortic region. There was tuberculous inflammation of the soft tissues of the aorto iliac region and the local lymph nodes. In all, the granulation tissue was extensive but just stopped at the level of the diaphragm. The lungs were heavily involved. In other organs the disease was minimal.

The aorta showed an inflammatory reaction of the adventitia (Figs. 18, 19). In the media, the inflammatory process produced focal destruction and vascularization. The elastic fibers were destroyed (Fig. 20). The intima showed marked proliferative thickening almost completely occluding the lumen. (Figs. 21 and 22). Another interesting feature was that when a segment of circumference of the aorta was involved the intimal

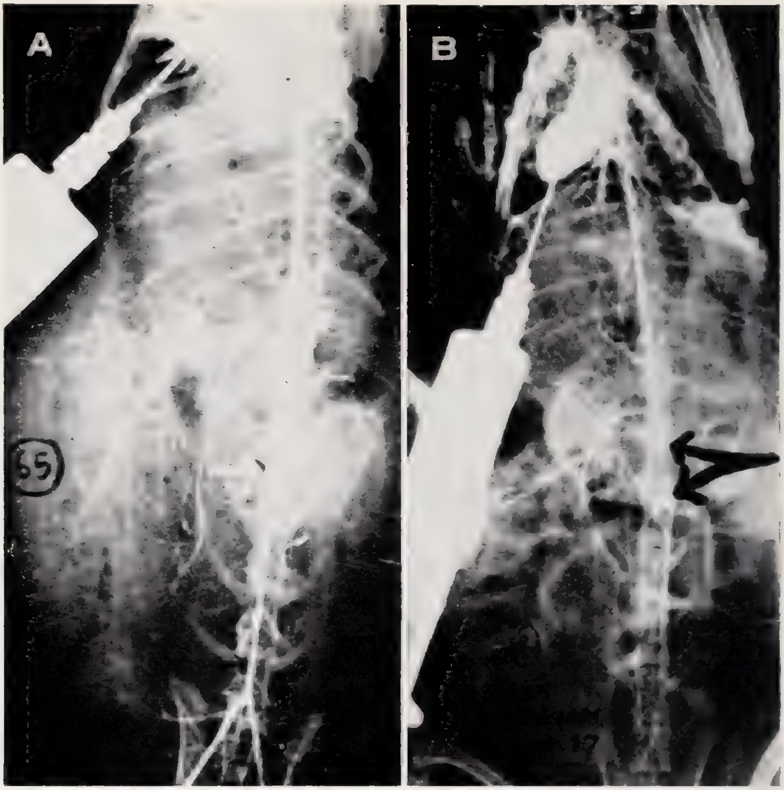

FIG. 15a. and b. A.P. and lateral view aortograms in a rabbit injected with human tubercle bacilli in the periaortic tissue showing constriction of the affected segment of the aorta.

change was restricted to that particular segment. In instances where inflammation was present, the intimal proliferation was seen involving the entire circumference.

Six rabbits were sacrificed after two and one-half to five months. In four of these animals, an identical picture was produced.

8.) *Human tubercle bacilli:* Typical and definitive changes were produced in all three animals. In two instances, tuberculous inflammation of significant degree was seen in the periaortic region. One showed typical infiltrative changes in the adventitia and moderate thickening of the intima. The media was not involved. The changes were similar to those caused by the bovine bacillus but, in general, were slightly less marked.

9.) *Chemicals:* None of the rabbits injected with chemicals in the periaortic region showed any remarkable or specific changes. One rabbit with multiple injections showed some inflammatory reaction in the adventitia but the picture did not resemble that of nonspecific aortitis.

Discussion

Nonspecific aortitis has such diverse manifestations that for about 50 years it has been called by many names that either honored a physician or described the clinical complex.

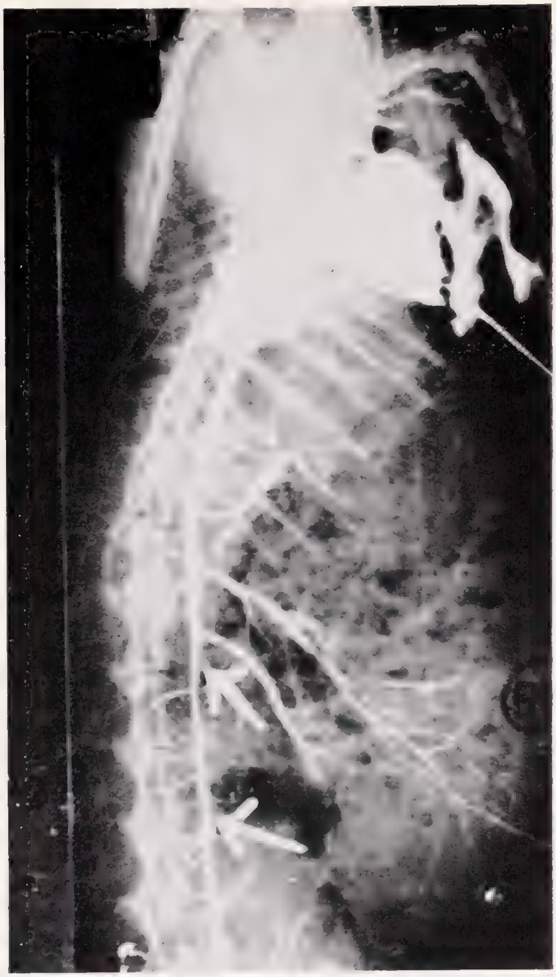

FIG. 16. Lateral view of an aortogram showing constriction of the abdominal aorta in a rabbit injected with B.C.G.

In the middle 1960's we began to realize that the division of the disease into several distinct clinical varieties (aortic arch syndrome, middle aortic syndrome, renovascular hypertension) as described in different parts of the world was not entirely correct and that combinations could be seen in the same geographical location. Pulmonary artery involvement is common in Scandinavian cases (8, 17), but has also been reported from India (5). In our own series, we have patients in whom all branches of the aortic arch were occluded exactly as "pulseless disease" cases described from Japan.

The pathology of all cases, no matter from where reported, is identical. Inflammation of periadventitial tissues makes postmortem separation of the aorta difficult. The affected aorta is rigid and the normal shiny external appearance of the adventitia is lost. Aneurysmal changes are seen in about 25 percent of cases. The lumen is considerably reduced by thickening of the wall (Fig. 9). Histologically the adventitia is markedly infiltrated with collagenous material. The vasa vasora show perivasal small round cell infiltration, but plasma cells

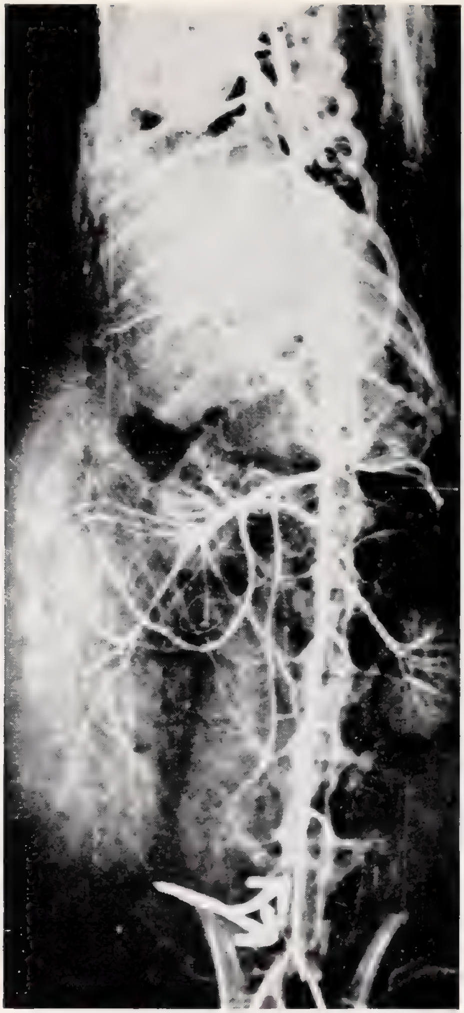

FIG. 17. Lateral view of aortogram showing constriction of aorta at bifurcation in a rabbit injected with bovine tubercle bacilli.

are absent. Later, the vasa vasora show obliterative changes and dense fibrosis. Variable amounts of destruction of the medial elastica are seen with or without formation of aneurysms. Sometimes productive granulomatous lesions with large collection of lymphocytes and occasional giant cells are also seen. Generally, however, the cellular reaction is very scanty. The disease affects the intima where severe proliferative fibrosis, atheromatous changes, occasional calcification, and thrombosis are seen in advanced cases.

The picture differs from syphilis which does not produce constrictions of the aorta. In syphilis, there are masses and linear streaks of both lymphocytes and plasma cells around the vasa vasora, plasma cells are diagnostically important, and there are many foci of inflammatory cells with necrosis and destruction of the elastic tissue.

In atherosclerosis, the changes first develop in the intima where a patch of yellowish material first appears. This ulcerates so that thrombi are deposited.

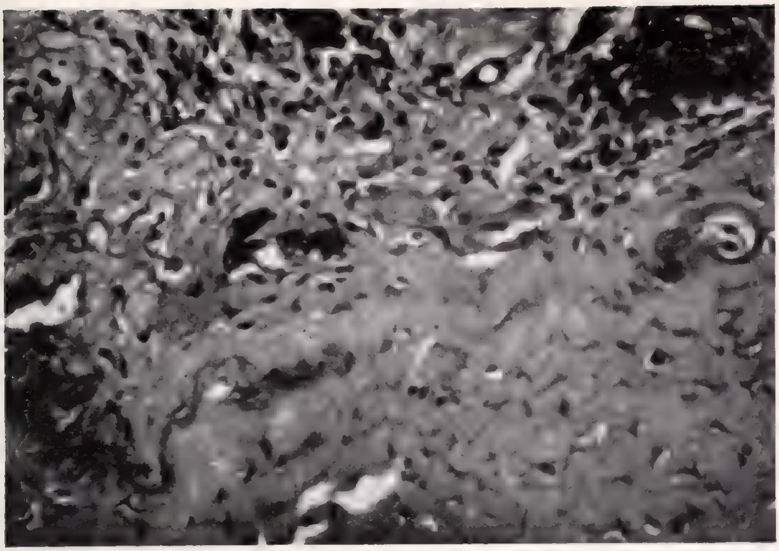

FIG. 18. Adventitial inflammation spreading to media.

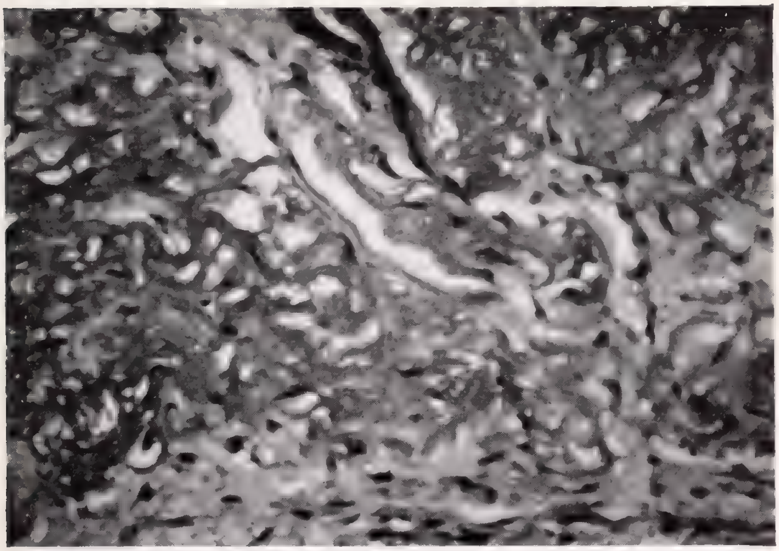

FIG. 19. Focal destruction and vascularization of the media.

Calcification follows and then dissection occurs. Histologically, there is swelling or increase of the ground substance of the intima, disintegration of elastic fibers, and deposition of lipids in the deeper part of the lesion. Intimal hemorrhage is common, and this enlarges the atheromatous plaque to intensify the process.

Polyarteritis nodosa, thromboangiitis obliterans, and giant cell arteritis, although belonging to a broad group of immune arteritides can be readily differentiated from nonspecific aortitis. Polyarteritis nodosa affects the arteries of the

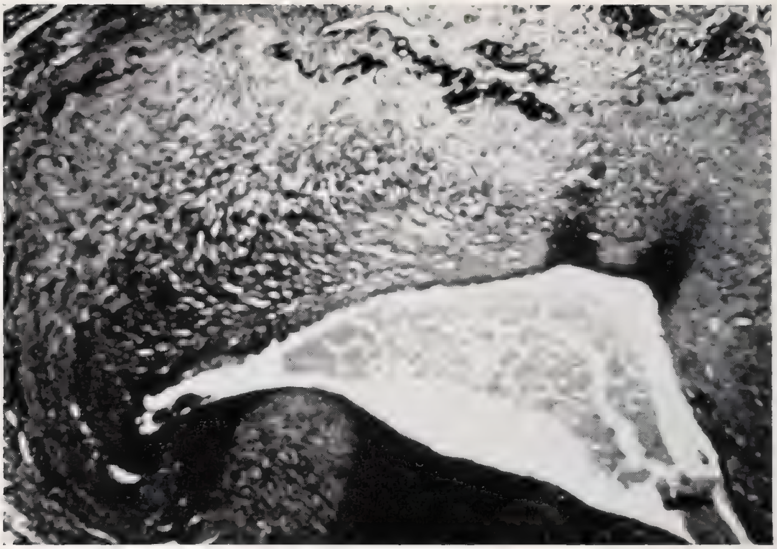

Fig. 20. Destruction of medial elastica.

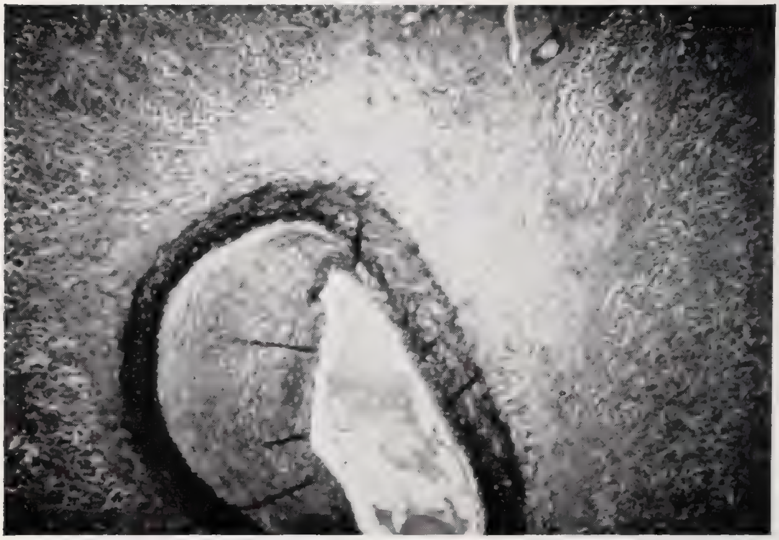

Fig. 21. Tuberculous inflammation around the aorta. Marked intimal proliferation.

gastrointestinal tract, kidney, heart, brain, lungs and skin. It is not known to affect the aorta. Nodules are found along the course of affected arteries which gives the disease its name. Histologically, there is fibrinoid necrosis, first of the media and later, of the other coats. Fragmentation of the elastica takes place and inflammatory cell infiltration involves all coats, unlike the picture seen in aortitis. At first the cells are neutrophils and eosinophils.

Giant cell arteritis predominantly involves medium-sized muscular arteries, like the temporal, but is also known to affect the aorta. However, the histologic picture is characterized by the presence of many giant cells and eosinophils.

There is a thickening of the intima due to formation of a zone of loose cellular connective tissue. Both these features are absent in aortitis, though occasional giant cells are seen along with fragmentation of the elastic fibers.

Thromboangiitis obliterans mainly affects the arteries of the inferior extremities. There is acute inflammation of the vessel wall with polymorphonuclear

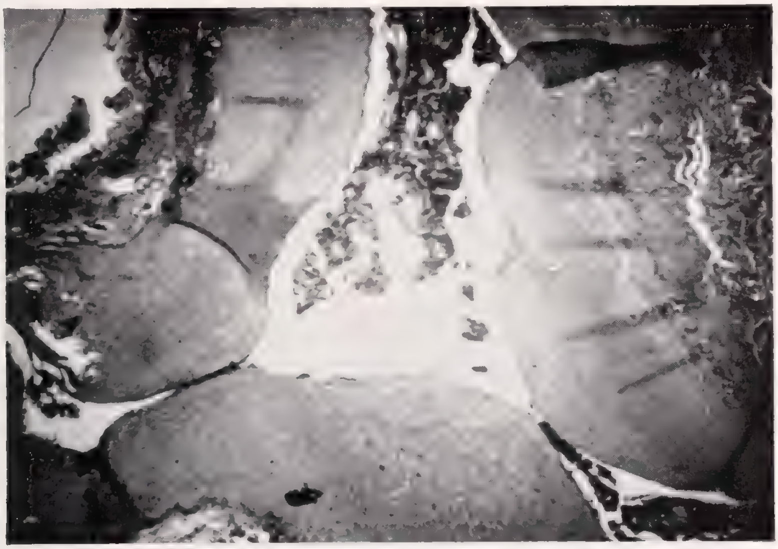

FIG. 22. Intimal hypertrophy with irregularity of lumen.

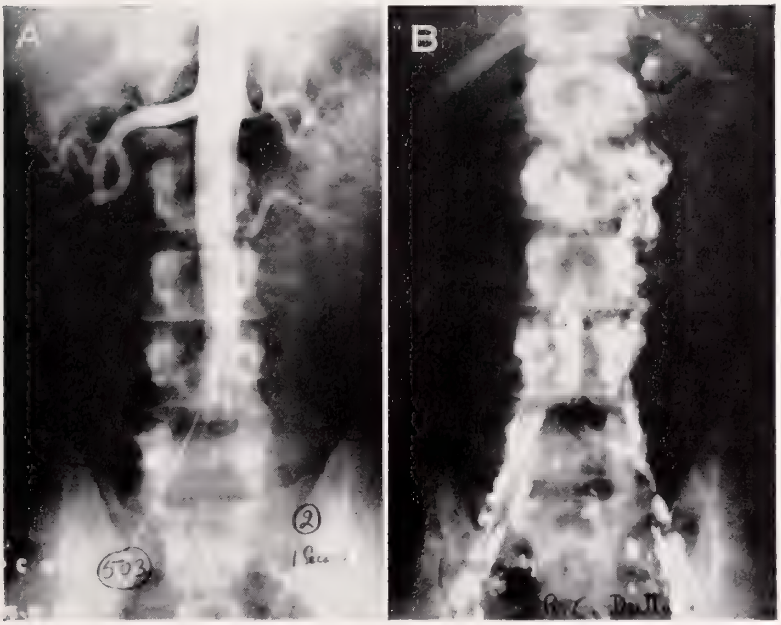

FIG. 23a. and b. Aortogram on left shows (left) renal artery stenosis. Postoperative lymphangiogram shows destruction of an adjacent lymph node not removed at operation.

invasion of the resultant thrombus. Later these foci heal, and thickening of the intima is left with some recanalization and residual sclerosis of the vessel wall.

Nonspecific aortitis, therefore, has a separate and distinctive histopathologic picture, although there are occasional cases where borderline features are suggestive of other types of arteritis.

That this condition is an immune reaction to some antigen is accepted by most authors. Association of tuberculosis in our own clinical material is very high. In 80 cases seen so far at least 30 had a clinically demonstrable lesion, and this cannot be dismissed as purely accidental. Moreover, in most of our cases the associated tuberculous focus was just adjacent to the diseased segment. This juxtaposition is too critical and constant to be dismissed casually. It is interesting to recall an early case which drew our attention to this factor. A young male presented with severe hypertension, and aortography revealed severe left renal artery stenosis with an atrophic kidney. Nephrectomy was performed and at operation a large caseating lymph node was found in close proximity to the left renal artery. The artery on histological examination showed typical changes of arteritis, and the lymph node showed tuberculosis. Subsequent to the operation, another juxtarenal lymph node, left untouched at operation, was shown by lymphangiography to be partly destroyed (Figs. 23a, 23b). This is an example of segmental arteritis affecting a single branch as opposed to aortitis which affects the aorta as well as several of its branches. The microscopic picture is, however, identical, and the juxtaposition of tuberculous nodes is very similar.

The histology of this type of nonspecific aortitis resembles that seen in the meningeal vessels of tuberculous meningitis. In the latter condition there is a marked response to tuberculous inflammation in the nature of fibrous intimal proliferation, but actual tuberculous giant cells are rarely seen in the vessel wall. The medial lesions appear to be secondary to changes in the vasa vasora and the intima, and the medial granulomatous lesions may be a foreign body reaction to degenerated fragmented elastica. Some of these changes may merely reflect a response to lymph blockage of the wall of the artery. Histologic evidence of blockage of lymph flow, especially if it affects the efferent vessels of the regional lymph nodes, has been amply documented (26), as a characteristic sieve-like appearance of nodes in cut section.

The high incidence of associated tuberculous disease, especially of the juxtaarterial and paraaortic lymph nodes as found in our experience, together with the known response of the arterial wall (at least in small sized meningeal vessels) to surrounding tuberculous inflammation, pointed to one clinically inescapable surmise—tuberculosis may play an important and perhaps a definitive role in the genesis of this condition.

Our experimental studies have encouraged us in this belief. With horse serum protein antigen injections only three out of seven rabbits showed any detectable histological response in the wall of the aorta, and these changes were very mild with only slight intimal changes. In 28 rabbits injected with protein extracts of tubercle bacilli (old tuberculin, P.P.D., Freund's adjuvant), only one specimen showed a very mild and similar change. In three rabbits injected with live streptococci not one showed any change, although prior sensitization was not performed in these animals.

In contrast to these, with periaortic injections of live tubercle bacilli, B.C.G. produced a change in only two out of 22 rabbits, but live bovine Mycobacteria, showed a picture in seven out of ten rabbits which was identical with the histopathology of the disease in man. A similar result was obtained when rabbits were injected with a human strain of Mycobacterium; three out of six rabbits injected showed an identical histopathology. These findings in our opinion are significant in linking this disease with tuberculous infection.

It may be possible to put this to test clinically, as we are now trying to do, by obtaining patients in whom the disease in the aorta is minimal and placing them on intensive antituberculous therapy designed to arrest or eradicate the disease. The natural history of this disease is, however, bizarre and variable, and only a long-range, controlled clinical study of a large series if patients can provide satisfactory answers.

Summary

Some aspects of our experience with nonspecific stenosing aortitis in India are described, together with our discovery of its association in our area with tuberculosis.

The histologic picture in this condition resembles that of the arterial pathology of tuberculous meningitis. The possibility of this condition being an immune arteritis caused by Mycobacterium tuberculosis has been explored experimentally using periaortic injections in sensitized rabbits. Experimental results and other collateral evidence support the premise that tuberculosis plays an important role in the pathogenesis of nonspecific aortitis. The disease pattern has been reproduced experimentally in sensitized animals. It is postulated that juxtaaortic (or juxtaarterial) lymph node tuberculosis with lymphangitis and blockage of lymphatic flow is directly concerned in producing the arteritis, either through contiguity and retrograde flow of lymph and/or an immune mechanism.

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The Effect of Hyperventilation on Pulmonary Surface Activity*

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Pulmonary surfactant plays an important role in the mechanics of respiration by promoting alveolar stability and by reducing the work of breathing (1). Schultz (2) first suggested that mechanical stress of the alveolar lining could change its surface properties. He found that overinflation of the lungs caused cytoplasmic degeneration of the alveolar cells. Lung compliance, as measured from pressure-volume relationships, has been shown to be reduced following prolonged intermittent positive pressure ventilation (3), hyperventilation (4), and surgical anesthesia (5). The fall in compliance which is seen following hyperventilation during intermittent positive pressure ventilation has been shown to be related to the tidal volume and the duration of ventilation (6).

Pressure-volume relationships depend to a large extent on the total elastic recoil of the lungs, so that evaluation of changes occurring in them must take account of the individual forces contributing to the total elastic behavior of the lungs. Such forces include tissue inertia, resistance to deformation, tissue elaticity, and surface tension forces (1). Inertial and tissue resistance forces in the lung can be considered insignificant under static conditions (7, 8). Alveolar tissue has inherent elasticity which is frequency- and force-dependent (9), but its contribution to total lung elasticity is small compared with that of surface tension forces. Hyperventilation has been shown to have no effect on lung tissue elastic forces (4).

The stability of bubbles expressed from the lung has been used as an index of pulmonary surface activity (10–14). Good correlation has been found in respiratory distress syndrome where deficiency of pulmonary surfactant is a typical feature between the reduction in lung compliance, the increased surface tension of extracted lung material and the reduction in the bubble stability ratio (15). The stability ratio of lung bubbles is the ratio of the final surface area to the initial surface area.

The suggestion has been made that hyperventilation causes a reduction in the amount of effective pulmonary surfactant (16). This paper reports the results of a study of pulmonary surface activity following hyperventilation in living anesthetized guinea pigs.

Methods

Thirteen guinea pigs (G.U. Physiol/Biochem strain) were anesthetized with intraperitoneal pentobarbital sodium (50 mg/kg). A tracheotomy was performed and the trachea cannulated with a "Y" tube. Each animal was assigned

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to one of the four groups: 1) controls in which there was no artificial ventilation; 2) hyperventilation for five minutes; 3) hyperventilation for ten minutes; and 4) hyperventilation for fifteen minutes. The animals were ventilated with positive pressure inflation by a Palmer small animal pump at a constant rate of 32 respirations per minute and with a tidal volume equal to three-quarters of the calculated vital capacity. At the end of the ventilation period (in the case of the control animals this was immediately following tracheotomy and cannulation of the trachea) the side arms of the "Y" tube were clamped and a sternum splitting incision quickly made. The anterior chest wall was widely separated and the trachea, lungs, heart, and great vessels were dissected en bloc. The lungs were then allowed to deflate slowly by slackening one of the clamps on the "Y" tube. The heart and great vessels were then carefully dissected. The "Y" tube was suspended vertically from a clamp stand. The pleural surface of the suspended lungs were bathed frequently with normal saline at 37°C throughout the entire procedure.

Method of performing pressure-volume maneuvers

One side arm of the "Y" tube was connected to a Greer electromanometer (Mercury Electronics, Scotland) while the other was connected to a calibrated syringe. Pressure as measured by the electromanometer was recorded on a pen recorder. Successive slow injections of 1 ml of air were made, allowing one minute between each step for equilibration of the static recoil pressure within the lungs. The maximum inflation volume, i.e., the total volume of air within the lungs, was taken as having been reached when the pressure started to rise steeply for a small volume increment. Deflation was effected by an exactly reversed procedure. Three pressure-volume maneuvers were performed on each set of lungs from each animal. On completion of the recording of the pressure-volume relationships the lungs were inflated under saline to check for air leaks.

Method of measuring lung compliance

Lung compliance was measured from the deflation curves of the pressure-volume relationships by computing for each animal the mean ratio of volume to pressure. Six sets of values were extracted from each curve at points corresponding to pressures of 5, 10, 15, 20, 25 and 30 cms of water.

Lung stability index

An index of the stability of the lung can be obtained from the deflation part of the pressure-volume relationship (17). The human lung index is given by $L = 2V_5 + V_{10} - 3V_0/2V_{max} - 2V_0$, where V_0, V_5, V_{10} are the lung volumes at 0, 5, 10 cms H_2O pressure and V_{max} is the lung volume when the lungs are maximally inflated. Since the pressure-volume relationship for the lungs of small mammals is characterized by relatively large lung volumes at zero pressure, Gruenwald suggests that the stability index for this group is given by $L = 2V_5 + V_{10}\ 2V_{max}$. Normal values for human lungs range from 0.8–1.4 and for small mammals from 0.9–1.2.

Bubble stability ratio method of obtaining lung bubbles

The bubble stability ratio of lung bubbles is calculated by dividing the sum of the squares of the diameters measured exactly 20 minutes after they have been expressed from the lung, by the sum of the squares of the initial diameters. Lung samples were obtained from each of the animals studied after completion of the pressure-volume maneuvers. These samples were in most cases whole lobes and were taken from the upper and the lower lobes of both lungs, thus giving four samples from each animal. The lung samples were inflated with air from a syringe fitted with an 18-gauge needle. A small piece of lung tissue was grasped with a pair of forceps. Lung bubbles were squeezed into a drop of aerated distilled water on a glass cover slip and a hanging drop preparation made. This was immediately viewed under a light microscope and a suitable field chosen containing about 20 bubbles. The light source was an infra-stage tungsten lamp which was only switched on during counting procedures.

Exactly one minute after the hanging drop preparation had been made, the diameters of the selected groups of bubbles were measured using an integrating eyepiece micrometer (Leitz, type K, magnification ×8). Repeat measurements of the diameters of the same group of bubbles in the same order of measuring were made after exactly 20 minutes. Continuous viewing of the bubbles between counting procedures was done using an angled light source, thus preventing any thermal expansion of the bubbles and also insuring that the same group of bubbles was counted. Eight hanging drop preparations were obtained from each animal, i.e., two from each area sampled. The groups of bubbles used for bubble stability measurement had in all cases diameters within the range 30–70u, as recommended by Seculic, Hamlin, Ellison & Ellison (13).

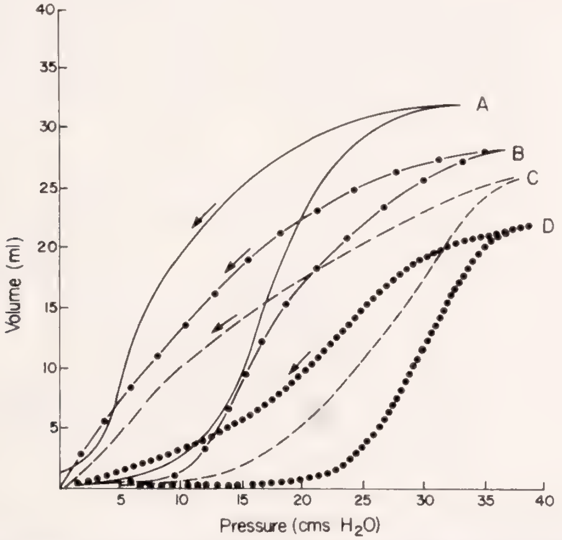

FIG. 1. Typical pressure-volume curves for: A. Control lungs; B. 5 min hyperventilation; C. 10 min hyperventilation; D. 15 min hyperventilation. The deflation part of each pressure-volume curve is arrowed.

Results

Pressure-volume relationships

Typical pressure volume relationships for each of the four groups of animals studied are shown in Figure 1. There was no significant difference between the pressure-volume relationships obtained for each animal within each group. In the control group the hysteresis between inflation and deflation curves was of similar magnitude, the opening pressures were similar ranging from 6–8 cms of water, the pressure required to maximally inflate the lungs was of similar magnitude ranging from 25.5–30.2 cms of water, and the total volumes of the lungs were similar ranging from 32–36 ml.

Following hyperventilation, hysteresis increased progressively with duration of hyperventilation. The deflation curve was less sigmoid in the hyperventilated groups than in the control. The opening pressure increased and the total volume of the lung fell progressively after hyperventilation. The mean opening pressures, mean pressures at total lung volume together with the mean total lung volumes are given in Table I for each of the four groups of animals.

Lung compliance

The values of lung compliance for each animal are given in Table II. The mean control value of compliance was 1.7 ml/cm of water. Hyperventilation reduced lung compliance so that after 15 minutes it was only 30% of the initial value found in the control group. There were significant differences between all four groups. Student "t" values and probabilities are shown.

Lung stability index

The values obtained for each group of animals are given in Table III. The mean value in the control animals was 0.57. Hyperventilation caused the stability index to fall progressively so that after 15 minutes it was 17% of the control value. The differences between each group were highly significant.

Bubble stability ratio

Table IV shows the bubble stability ratios for each of the areas sampled in each of the four groups as means. There was no significant difference between

TABLE I

The Mean Opening Pressure in Cms. of Water, the Mean Pressure at Total Lung Volume in Cms. of Water and the Mean Total Lung Volume, for Each of the Four Ventilation Groups

	Opening Pressure (±1 SD)	Pressure at Total Lung Volume (±1 SD)	Total Volume of Lungs (±1 SD)
Controls	7.2 ± 0.3	27.4 ± 0.6	34.3 ± 0.2
Hyperventilation for 5 minutes	11.5 ± 0.2	36.2 ± 0.4	28.5 ± 0.1
Hyperventilation for 10 minutes	15.4 ± 0.2	42.0 ± 0.3	26.0 ± 0.2
Hyperventilation for 15 minutes	24.6 ± 0.4	44.0 ± 0.3	23.1 ± 0.2

the stability ratios of the different areas in any of the four groups. The difference between the overall mean stability ratios for each of the groups was highly significant, as was the difference between groups for each sampling area. Student "t" values and probability levels are given. Hyperventilation reduced the bubble stability ratio from a mean value in the control group of 0.84 to 0.74 after 5 minutes to 0.71 after 10 minutes to 0.6 after 15 minutes; this represents a reduction of 23% in the bubble stability ratio after 15 minutes hyperventilation. Figure 2 shows the effect of hyperventilation on bubble stability ratio, lung compliance and lung stability index. The curves shown are drawn through the mean values in each ventilation group.

Discussion

It is evident from the pressure-volume relationships of the control lungs obtained in this study that the guinea pig is similar in this respect to other mammals. The values which were obtained for lung compliance are similar to those previously reported by others for guinea pig lungs (18, 19). There are no

TABLE II

Values of Lung Compliance for Each Animal in ml/cm. of Water

	Control	Hyperventilation ± 1 SD for 5 minutes	Hyperventilation ± 1 SD for 10 minutes	Hyperventilation ± 1 SD for 15 minutes
	1.77 ± 0.2	1.40 ± 0.13	1.02 ± 0.34	0.60 ± 0.22
	1.65 ± 0.32	1.32 ± −.10	0.67 ± 0.18	0.46 ± 0.14
	1.54 ± 0.18	1.46 ± 0.21	0.83 ± 0.26	0.50 ± 0.17
	1.88 ± 0.46			
Mean ± 1 SD.......	1.71 ± 0.29	1.39 ± 0.1	0.84 ± 0.21	0.52 ± 0.17
Student t values + probabilities	$t_{19} = 3.27$ $P < 0.01$	$t_{16} = 7.78$ $P < 0.001$		$t_{16} = 4.11$ $P < 0.001$

TABLE III

Values of Lung Stability Index for Each Animal

	Control	Hyperventilation ± 1 SD for 5 minutes	Hyperventilation ± 1 SD for 10 minutes	Hyperventilation ± 1 SD for 15 minutes
	0.54 ± 0.08	0.46 ± 0.05	0.28 ± 0.02	0.09 ± 0.01
	0.60 ± 0.02	0.51 ± 0.05	0.31 ± 0.04	0.11 ± 0.06
	0.58 ± 0.10	0.50 ± 0.01	0.34 ± 0.01	0.16 ± 0.04
	0.56 ± 0.06			
Mean ± 1 SD	0.57 ± 0.04	0.49 ± 0.03	0.31 ± 0.03	0.12 ± 0.04
Student t values + probabilities	$t_{19} = 5.67$ $P < 0.001$	$t_{16} = 18.0$ $P < 0.001$		$t_{16} = 12.39$ $P < 0.001$

TABLE IV

The Mean Bubble Stability Ratios for Each Area Sampled

Student "t" values and probabilities are given for the difference between the overall means of each of the ventilation groups.

	Controls ± 1 SD	Hyperventilation ± 1 SD for 5 minutes	Hyperventilation ± 1 SD for 10 minutes	Hyperventilation ± 1 SD for 15 minutes
Upper right	0.827 ± 0.028	0.732 ± 0.062	0.710 ± 0.032	0.655 ± 0.042
Lower right	0.830 ± 0.034	0.740 ± 0.016	0.721 ± 0.012	0.660 ± 0.031
Upper left	0.847 ± 0.022	0.734 ± 0.014	0.708 ± 0.022	0.642 ± 0.014
Lower left	0.845 ± 0.030	0.752 ± 0.040	0.718 ± 0.051	0.630 ± 0.020
Grand mean for whole lung n = 32	0.837 ± 0.032	0.739 ± 0.033	0.714 ± 0.025	0.645 ± 0.022
		$t_{62} = 5.06$ $P < 0.00$	$t_{62} = 3.26$ $P < 0.01$	$t_{62} = 4.68$ $P < 0.001$

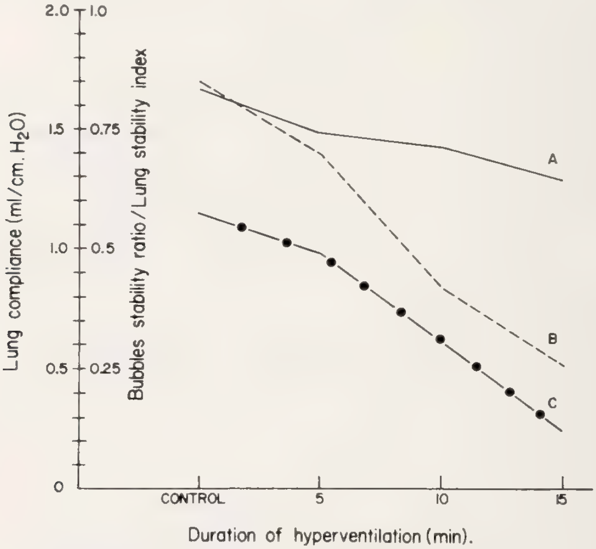

FIG. 2. Effect of the duration of hyperventilation on: A. Bubble stability ratio; B. Lung compliance; C. Lung stability index. The curves shown are drawn through the means for each of the ventilation groups.

previously described measurements of the stability index of guinea pig lungs. The stability index of rabbit lungs lies within the range 0.92–1.21 (17). The stability index of the control lungs of guinea pigs found in the present study was 0.57. This is in keeping with the consistent finding that lung compliance in the rabbit is higher than in the guinea pig. The relatively small range of stability index found in the present study might indicate that for the guinea pig, at least as an estimate of pulmonary surface activity, the stability index is a more accurate measure than lung compliance.

Hyperventilation reduced lung compliance and lung stability index, and decreased the total volume of the lungs to a degree which depended on the duration of hyperventilation. It also increased the opening pressure and the pressure required to maximally inflate the lungs. This would indicate that the factors which maintain the normal pressure-volume relationship were progressively altered following hyperventilation. These factors are generally considered to be of two types, those tissue elastic forces which have been shown to be unaltered by hyperventilation (4) and surface tension forces. One can conclude, therefore, that the surface tension forces have changed following hyperventilation in such a way that they maintain higher than normal tensions within the lung with the tendency to premature emptying.

Recent work suggest that following hyperventilation the alveolar volume, but not that of the alveolar ducts, is reduced. This work (20) which was a morphometric study of guinea pig lungs, indicated that following hyperventilation for 15 minutes the total alveolar surface area is reduced by 40 percent. Since pulmonary surfactant is effective at the alveolar surface it suggests that following hyperventilation there is a steady degradation of pulmonary surfactant. The finding that bubble stability ratios are reduced following hyperventilation, i.e., the bubbles tend to reduce in size more rapidly, implying a higher surface tension, is in keeping with this hypothesis, first proposed by McClenahan (1966) (16).

It is not suggested that there is a direct application of these findings to the clinical situation, since there can be few occasions when hyperventilation with a tidal volume of three-quarters of the vital capacity is practiced. Nonetheless, the progressive reduction in surface activity found in this study might indicate that following repeated overinflation of the lungs, e.g., during mechanically controlled ventilation, pulmonary surface tension forces will increase, thus promoting premature alveolar atelectasis. This may be a contributary factor in the production of postoperative atelectasis and hypoxia, especially when functional residual capacity is already reduced due to upper abdominal or chest wound pain.

Summary

The effect of gross hyperventilation on the pulmonary surfactant activity in the lungs of anesthetized guinea pigs is examined. Statistical analysis shows a significant increase in the surface tension forces in the alveoli indicating interference with the surfactant mechanism.

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The Partial Hospital as a Transition from Inpatient Treatment: A Controlled Follow-Up Study*

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Partial hospitals have emphasized primarily their roles as transitional facilities between inpatient and outpatient care (1–3) and as alternatives to inpatient hospitalization (4–8). Despite a rapid increase in the number of operating partial hospitals programs during the past decade (9), few controlled studies have been reported which assess the effectiveness of partial hospitalization (10–13). Without research and evaluation, as Guy and Gross have pointed out, any philosophical attractiveness of partial hospitalization or enthusiastic advocacy by its supporters is weakened (9).

This investigation, the second in a series on the utilization and effectiveness of partial hospitalization (7), focuses on what effect, if any, a predischarge period in the day or night hospital, as a part of the total period of hospitalization, has on the patient's future course.

A group of full-time psychiatric patients who used the partial hospital as a transitional step out of the hospital ("transitional group") was compared with a group of psychiatric inpatients who, although given passes prior to discharge, were sent directly from full-time hospitalization to the community ("inpatient group"). Seven variables were controlled in the two groups. Rehospitalization in a 24-hour setting during a two-year follow-up period was used as the principal criterion for measuring the effect of a period in the partial hospital prior to the return of the patient from the 24-hour service to the community.

Methods

This retrospective follow-up study was conducted using patients admitted to the inpatient services of The Mount Sinai Hospital Institute of Psychiatry during 1967 (14). The partial hospital (day or night) to which some patients were transferred prior to discharge operates seven days a week and has been described extensively in previous publications (7–9). It is located in the same building as the inpatient services, but on a separate floor. Space for occupation and recreational activities is shared with the inpatient services, but separate programs are maintained.

At the time of their hospitalization during 1967, patients, when transferred from the inpatient service to the partial hospital, moved from an environment where individual psychotherapy was the predominent treatment of choice to one where milieu and group therapy played the primary role and where individual therapy was an adjunctive treatment. These differences are similar to those reported by others who have developed partial hospital programs in institutions which have had previously existing traditional inpatient services (9, 15).

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Selection of Patients for Follow-up: The transitional group was selected from the 324 patients who used the partial hospital during 1967. Since this partial hospital emphasized direct admission as an alternative to inpatient hospitalization (7), the potential number of patients in the transitional group was small (N = 50).

The size of the available sample of transitional patients was decreased further during the matching process because of our desire to control for as many variables as possible. Thirty of these were matched successfully with 30 patients drawn from the entire inpatient psychiatric population of approximately 700 patients during 1967.

Seven variables were considered in the selection of the 30 matched pairs:

(1) Sex. Twenty-one (70%) of the pairs were female and nine were male. This is similar to the total psychiatric census at Mount Sinai of 68% female and 32% male (16).

(2) Age. The average age of the transitional group was 27.9 years compared to 26.6 years in the inpatient group. (p = NS at the .05 level using a student "t" test.

(3) Race. Race was included as a variable because of its importance in New York City as a barometer of socioeconomic level. Of the 30 pairs selected for study, twenty-six (87%) were white and four (13%) nonwhite (16).

(4) Marital Status. Patients were matched for marital status as a reflection of the home living arrangement after discharge, an important influence on the future course of any discharged psychiatric patient. Of the 30 pairs, 19 were single (63%), six were separated or divorced (20%) and five were married (16).

(5) Diagnosis. Primary diagnosis was matched using the 1967 Mount Sinai Diagnostic Index based on the "International Classification of Diseases" (6). This distribution of diagnoses is shown in Table I.

(6) Length of Mount Sinai Hospitalization. The average period of Mount Sinai hospitalization was 75.3 days for the transitional group and 71.0 days for the inpatient group. (p = NS at .05 level using a student "t" test). Patients in the transitional group spent an average of 21.2 days (28.2%) of their hospitalization in the partial hospital immediately prior to discharge.

(7) Disposition. A crucial factor in any follow-up is the type of aftercare treatment which the patient received. The 30 pairs were matched as follows: six (20%) to private individual psychotherapy; eleven (36.7%) to the Mount Sinai Aftercare Clinic for medication and individual therapy, nine (30%) to medical clinic primarily, and four (13%) received no aftercare treatment.

Data Collection: All patients included in this study were discharged in 1967. Data collection was begun at the end of 1969. Initially, a short questionnaire was mailed to each of the 60 patients requesting information concerning events

TABLE I

Diagnostic Classification

Diagnosis	Number of Pairs (N = 30)
Schizophrenia, paranoid type	12 (40%)
Schizophrenia, undifferentiated type	6 (20%)
Unspecified psychotic reactions	3 (10%)
Involutional psychotic reaction	1 (3%)
Depressive reaction	7 (24%)
Epilepsy	1 (3%)

since discharge. Failure to respond was followed by a second mailing. Eighteen questionnaires were returned. Phone calls were then made in an effort to locate the remaining 42 patients. Ten were reached by this method, bringing the total number reached through either of these direct methods to 28 (47%).

The remaining patients could not be located by mail or telephone. Consequently, the New York State Department of Mental Hygiene Data Bank (Albany, New York), which contains information on patients admitted to 24-hour hospitalization throughout the state, was consulted.

Results

Incidence of Rehospitalization: Table II displays the two-year rehospitalization record for the 30 matched pairs of patients. Seven patients in the transitional group were rehospitalized (23%) compared to eleven patients from the inpatient group (37%). This difference is not significant at the .05 level using a 2 × 2 Chi Square Analysis.

Patients in the transitional group who were rehospitalized were treated in the partial hospital for an average of 17.9 days compared to 22.3 for those who were not rehospitalized (p = NS at the .05 level using a student "t" test).

Interval between Discharge and Rehospitalization: The seven rehospitalized patients in the transitional group remained out of the hospital an average of 29.6 weeks (Range: 1–60 weeks) following discharge. The eleven rehospitalized patients from the inpatient group were out of the hospital an average of 18.4 weeks (Range: 1–72 weeks) following discharge. A student "t" test revealed no significant difference between these two means despite an indication that the group of patients who were treated in the partial hospital prior to discharge did not require rehospitalization as early.

However, when only the eight-week period following discharge was examined, the data (Table III) reveal that only one of the patients in the transitional group was rehospitalized ($N = 7$; 14%) compared to seven of the inpatient group ($N = 11$; 64%). This significant finding $X^2 = 4.22$; $p < .05$) suggests that the partial hospital was effective, on a short-term basis, in preventing the rehospitalization of patients on a 24-hour inpatient service.

Length of Rehospitalization: The patients in the transitional group were rehospitalized for an average period of 23.6 weeks (Range: 5–72 weeks) com-

TABLE II

Rehospitalization during Two-Year Follow-Up Period

	Transitional Group	Inpatient Group
Rehospitalized (N = 18)	7	11
Not Rehospitalized (N = 42)	23	19
Total	30	30

$X^2 = 1.27$; p = NS at the .05 level.

TABLE III

Interval between Discharge and Rehospitalization

	Transitional Group	Inpatient Group
Less than eight weeks (N = 8)	1	7
Greater than eight weeks (N = 10)	6	4
Total Number Rehospitalized	7	11

$X^2 = 4.22$; $p < .05$.

pared to 16.7 weeks (Range: 4–36 weeks) for the inpatient group. However, if one patient in the transitional group, who was rehospitalized for 72 weeks, is eliminated*, the average period of rehospitalization for the transitional group is lowered to 15.5.

Discussion

The use of the partial hospital as a transitional facility in the movement of a patient from inpatient to outpatient status appears to be at least as effective as hospitalization on a 24-hour inpatient service alone when rehospitalization during a two-year follow-up period is used as the principal criterion of effectiveness.

However, the data suggests that the partial hospital as a "transitional" facility is particularly effective in preventing rehospitalization during the first eight weeks after discharge. In this period, only one patient from the transitional group required rehospitalization in comparison to seven from the "inpatient" group. This is consistent with the findings of Herz et al (13) who have shown that patients treated in a day hospital may show significantly more improvement in some aspects of psychopathology than those treated on an inpatient unit during the early posthospital period.

Patients transferred to the partial hospital where they spend approximately 50% of the day living and/or working in the community, may do better initially because they receive support from the group oriented milieu of the partial hospital and the process of interaction with other patients in similar circumstances who are concerned with the problems of everyday living and work. The patients who prepare for discharge while on the inpatient service, on the other hand, continue to interact primarily with patients who are not going back and forth to the community and, consequently do no have as great an opportunity to share their experiences and problems. It is also true in our hospital that the passes of the inpatient group prior to discharge occur more irregularly and for briefer periods of time.

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* The other six patients in this group were rehospitalized for 5, 12, 12, 16, 16, and 32 weeks.

If the patients in the transitional group had spent a longer period of time in the partial hospital prior to discharge, would the incidence of rehospitalization have been decreased? Inconclusive evidence for the possibility is tentatively suggested by the data pertaining to the length of stay in the partial hospital. Those who were rehospitalized were treated in the partial hospital for an average of 17.9 days while those who were not rehospitalized remained for an average of 22.3 days.

All of the data presented would suggest that planners of partial hospital programs might consider using the partial hospital and its milieu for longer periods of time before discharge than would appear initially indicated; for intermittent use during periods of crisis after discharge; or as a partial hospital for less than five days a week or six hours a day for an extended period of time as a type of aftercare.* If these possibilities were utilized, the effectiveness of the partial hospital might be increased and the incidence of rehospitalization decreased.

Limitations of Study: More variables could have been controlled in the two groups of patients. The number was limited, however, by the amount of information available as well as by the need to keep the sample as large as possible so that collected data would be meaningful. Two variables, the incidence of previous hospitalization and the home living arrangement after discharge, are certainly important but were not included because of insufficient data. An effort was made to control for the latter variable, however, by including marital status as a factor in the matching of the pairs.

The limited questionnaire and phone responses (47%) and the reliance on a data bank, admittedly lacking in access to all rehospitalization data, contribute to questions concerning the completeness of the readmission data. Of those patients who had been rehospitalized, seven (39%) were located by questionnaire or phone while 11 (61%) were located through the data bank. Half of the remainder were located directly, and half through the data bank, (p = NS at .05 level, using a 2 × 2 Chi Square analysis).

Because the New York State Data Bank does not list hospitalizations out of state, it is possible that some incidents of rehospitalization may have been lost. However, even with this possibility, resulting in an upward adjustment of our figure of 37%, (the rehospitalization rate of the inpatient group), it would still compare favorably with the findings of Levenstein et al (17). Using a data collection system based primarily on personal contact, they found that 42% of the patients hospitalized on a voluntary inpatient service similar to our own were rehospitalized during a two-year follow-up period.

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* Such a program has been recently started at the Mount Sinai Day-Night Hospital.

The use of rehospitalization rates and related data to measure the effectiveness of the partial hospital has been questioned (18). Certainly, some patients who required hospitalization may not seek it and others who are rehospitalized may not require it. In a controlled study such as this, it is assumed that the two groups studied would be affected equally by these vagaries of the rehospitalization process. However, since the level of functioning and adjustment in the nonrehospitalized patient is an important measure of the effectiveness of a treatment program, the lack of data in this area is a deficiency of the study.

Summary

Thirty patients who were treated in the partial hospital during the transition from inpatient to outpatient status were matched using seven variables with 30 patients who were treated on an inpatient service and discharged directly to outpatient treatment to measure the effectiveness of the partial hospital as a transitional facility in the spectrum of psychiatric treatment.

These data support the conclusion that a treatment philosophy which utilizes the partial hospital to help the patient move out of the hospital is at least as effective, in terms of incidence of rehospitalization during a two-year post-hospital period, as the treatment program which keeps the patient on the inpatient service until the time of discharge. Furthermore, there is evidence which suggests that partial treatment may exert its greatest effect in preventing rehospitalization during the period immediately after discharge from the hospital (i.e., the first two months).

The limitations of this type of retrospective investigation have been discussed in detail. However, we believe that these data may help to answer questions which have occurred regarding the effectiveness of partial hospitalization.

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Fatal Infections Associated with Mycoplasma Pneumoniae: Discussion of Three Cases with Necropsy Findings

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Introduction

The mycoplasmatales, formerly known as pleuropneumonia-like organisms (PPLO), have been receiving increasing attention in the medical literature (1–6). In 1962 Chanock et al established Mycoplasma pneumoniae as an important causal agent of the syndrome of primary atypical pneumonia (7). However, the role of M. pneumoniae in nonrespiratory infections is at present unclear. Mycoplasma pneumoniae has been implicated etiologically in cases of arthritis (8), myocarditis (9), pericarditis (9), meningoencephalitis (10), vesiculo-pustular dermatitis (11), and the Stevens-Johnson syndrome (12).

The course of M. pneumoniae respiratory infections is usually benign and deaths rarely occur (1, 13). During the past year we treated three patients with overwhelming fatal illnesses and rising mycoplasma complement fixation titers. We report these cases and discuss the pathogenetic role of M. pneumoniae in these patients.

Methods

The three patients were hospitalized at The Mount Sinai Hospital in New York City. Culture specimens were processed by the diagnostic microbiology laboratory of the hospital using standard techniques. Cultures were not obtained for mycoplasmae. Viral isolations and serologic studies for mycoplasmae, including the mycoplasma complement fixation test, Streptococcus MG and cold agglutinins were performed by the diagnostic virology laboratory of the hospital. Viral serologic studies were performed at The Mount Sinai Hospital Department of Microbiology and confirmed by the New York City Department including the mycoplasma complement fixation test, Streptococcus MG, and postmortem examinations by the Department of Pathology of The Mount Sinai Hospital.

Report of Cases

Patient 1. A 55-year-old Caucasian woman was admitted to The Mount Sinai Hospital on August 14, 1969, with inflammation and edema of the left breast, axilla, and arm. This patient was enjoying her usual state of good health until approximately four days prior to admission when she noticed pain in the left axilla followed soon thereafter by fever. The patient had been on vacation in the Catskill Mountains area of New York State four weeks prior to admission. She denied local injury to her forearm and insect bites. She visited her private physician who noticed tender adenopathy of the left axilla and supraclavicular space. The patient was treated with Mysteclin F for two days without success and on the

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4th of August she was admitted to a local hospital. On admission, two raised and tender patches of erythema on the left forearm with lymphangitic streaks were noted. She was begun on oral ampicillin and the erythema slowly regressed. However, on the third hospital day she developed redness and warmth in the axilla, spiking fever to 104°F, and a white blood cell count (WBC) of 18,000/mm^3 with neutrophilia. The erythema was now brawny and involved the axillary portion of the left breast. The patient was given 20 million units per day of intravenous penicillin and tetracycline, 250 mg IM every six hours. On the eighth day of her illness, she had extensive erythema and induration of the left breast and chest wall. Lymphangitic streaks extended from the left axilla to the breast. A consultant felt that phlebitis was present. Penicillin and tetracycline were discontinued at this time and chloramphenicol, 3 gm per day, and erythromycin, 2 gm per day, were substituted and radiotherapy was begun. The dosage of radiation is not known. The lupus erythematosus (LE) cell preparations, VDRL test, febrile agglutinins, ASLO, CRP, SGOT, SGPT, bilirubin, stool culture, chest film, intravenous pyelogram, radiographic bone survey, and cervical spine examination were normal. An upper gastrointestinal series revealed a small hiatal hernia. Mammography showed a well-circumscribed nodule at the inferior aspect of the left breast. The erythrocyte sedimentation rate (ESR) was 82 mm/hr (Westergren); the white blood cell count ranged from 18 to 24,000/mm^3 with neutrophilia; prothrombin times (patient/control) were 15/12 and 18/12 seconds; and the alkaline phosphatase was 6 Bodansky units. Due to progression of the skin lesions and unremitting fever, the patient was transferred to The Mount Sinai Hospital. Physical examination at The Mount Sinai Hospital revealed a pulse of 140 beats per min, respirations of 30 per min, blood pressure of 150/50 mm Hg, and a rectal temperature of 101.8°F. The patient appeared acutely ill and was confused, complaining of pain in the left axilla. There were fine bibasilar rales and a grade 2/6 systolic murmur was heard along the left sternal border. Over the left forearm there were noted a palpable venous cord, erythema and pitting edema. There was brawny erythema over the lateral aspect of the left breast extending into the axilla. The left supraclavicular area was indurated and full but no discrete nodes were palpable.

Initial laboratory data included a white blood cell count of 17,200/mm^3 with 89% neutrophils and 2% band forms; platelet count, 327,000/mm^3; hemoglobin (Hgb), 9.4 Gm/100 ml; hematocrit (Hct) 28%. Chest roentgenogram showed diffuse infiltration of the left lung and the urinalysis was normal. It was felt that axillary vein thrombosis was present as well as cellulitis and lymphangitis, and therapy with heparin, cephalothin, and streptomycin was begun. Lumbar puncture revealed clear spinal fluid without cells; glucose, 90 mg/100 ml; and protein, 21 mg/100 ml. The tularemia slide agglutination titer was 1:80 but repeat titer the next day was negative. The inflammation of the left forearm began to subside and almost disappeared by the second day after admission. However, inflammation of the left chest wall and the lateral aspect of the breast remained. The patient became increasingly irritable and confused. Chest x-rays done two days after admission revealed bilateral interstitial infiltration. The patient was dyspneic with a respiratory rate of 40/min. without overt cyanosis, although the arterial P_{O_2} was 54 mm Hg and the P_{CO_2} 35 mm Hg. The patient remained febrile and on the sixth hospital day underwent a left-sided thoracentesis. Clear amber fluid was aspirated containing 2600 white cells/mm^3 of which 13% were neutrophils, 3% eosinophils, and 4% lymphocytes; the rest of the cells were lymphocytoid-like with vacuoles. Binucleated cells were seen as well. Examination of bone marrow aspirate showed erythroid hyperplasia. On the eighth hospital day, isoniazid (INH), 100 mg three times a day, and ethambutol, 400 mg three times a day, were begun. Cephalothin was discontinued and streptomycin was decreased to 0.5 gm per day. Chest films again revealed acute interstitial pneumonitis, the etiology of which was undetermined. Liver biopsy revealed nonspecific reactive hepatitis. Two weeks after admission the patient underwent open lung biopsy. Lung tissue was obtained for pathology, and viral and bacterial cultures. Microscopic examination showed interstitial pneumonitis with infiltration of macrophages. Cultures of the lung for fungi, bacteria, mycobacteria and viruses were negative. The patient remained confused and febrile with increasing respiratory distress. On the 18th hospital day, gentamicin was begun but did not favorably alter the clinical course. On September 6, 1969, intravenous mechlorethamine hydrochloride therapy was given for possible lymphoma. Steroid therapy was begun, but the patient deteriorated and had a cardiac arrest on September 8, 1969. Attempts at resuscitation were unsuccessful. The mycoplasma complement fixation titer rose from <1:8 to 1:32. Serologic studies on paired sera were negative for adenoviruses, influenza A & B, parainfluenza 1–3, psittacosis-lymphogranuloma group, Herpes hominis, cat-scratch fever, Q fever, toxoplasmosis, histoplasmosis, and cytomegalovirus.

Autopsy revealed diffuse interstitial pneumonia with some fibrosis of the lung. There were edema and thickening of the alveolar septa, and an increase in reticular material with accumulation of lymphocytes, plasma cells and histocytes within the septa. The presence of epithelial cells within the alveoli and terminal air passages simulated the picture seen in desquamative interstitial pneumonitis. A recent thrombotic occlusion of the left main pulmonary artery was responsible for death.

Patient 2. A 23-year-old Negro man from Trinidad was admitted to The Mount Sinai Hospital January 20, 1971 with fever and cough productive of yellow sputum. At 6 years of age, the patient had rheumatic fever with polyarthritis and a heart murmur for which he was hospitalized for two and one-half months in Trinidad. He was asymptomatic until one month prior to admission when he developed general malaise, anorexia, and cough productive of grayish sputum. Five days prior to admission to the Elmhurst General Hospital, he was seen by a private physician in Trinidad who gave him some "pills and an injection." Ony day later he developed increasing cough with yellow sputum and fever to 104°F. Hemoptysis occurred one day prior to admission. There was no history of exertional dyspnea, and, in fact, the patient stated that he had been playing soccer until the onset of this illness.

Physical examination on admission to the Elmhurst General Hospital revealed a dyspneic and slightly pale Negro man in acute distress. His rectal temperature was 104.2°F; pulse 120 beats per min and regular; blood pressure 120/40 mm Hg; and respiration, 24 per min. Rales were heard at both lung bases and the left hemithorax was enlarged. A systolic thrill was felt over the cardiac apex and a diastolic thrill at the base. A blowing grade 4/6 diastolic murmur radiating throughout the precordium and a grade 3/6 ejection type systolic murmur were heard in the aortic area; a grade 5/6 holosystolic murmur was present at the apex. The liver was palpable 2 cm beneath the right costal margin at the mid-clavicular line, and hepato-jugular reflux was observed. The electrocardiogram showed sinus tachycardia and left ventricular hypertrophy. Chest x-ray revealed cardiomegaly, an infiltrate in the right mid-lung field and slight congestion of the left lung. Admission laboratory data included hemoglobin, 10 Gm/100 ml; white blood cell count, $11,800/mm^3$ with 85% neutrophils and 3% band forms; and a urinalysis which showed 2+ protein and numerous red blood cells per high power field.

The patient was begun on 24 million units of penicillin and 1 Gm streptomycin per day. Sputum culture yielded pneumococci and group A beta hemolytic streptococci. Examination of sputum smears for acid fast bacilli and a skin test (second strength PPD) for tuberculosis were negative. On the second hospital day intravenous oxacillin, 12 gm per day, was begun. However, all blood cultures were negative and oxacillin was discontinued 3 days later. The patient remained febrile with daily fever spikes to 103°F, had hemoptysis and increasing congestive heart failure. Digoxin and diuretics were administered. Laboratory studies showed a serum sodium, of 126 mEq/liter; potassium 5.4 mEq/liter; blood urea nitrogen (BUN), 30 mg/100 ml, rising to 55 mg/100 ml; creatinine 1.3 mg/100 ml rising to 2 mg/100; serum protein of 7.5 Gm/100 ml with an albumin of 2 Gm/100 ml and a gammaglobulin of 2.5 Gm/100 ml; cholesterol, 90 mg/100 ml; alkaline phosphatase, 75 international units; total bilirubin 0.8 mg/100 ml; CPK, 470 international units; LDH, 700 international μunits; SGOT, 500 international units; and prothrombin time (patient/control), 15/13 seconds. The ESR on admission was 22 mm per hr and rose to 104 mm per hr by the 5th day. A sickle-cell preparation and examination of cerebrospinal fluid were negative. The white blood cell count increased to 23,000/mm^3 with 14% band forms. The reticulocyte count was at 5%; serum iron, 53 μg/100 ml with a total iron binding capacity of 248 μg/100 ml; and haptoglobins, 180 mg/100 ml. Cold agglutinin titers were negative; the Strep. MG titer, 1:20; VDRL and latex fixation tests were negative. A bone marrow aspirate showed reactive changes.

Because of increasing congestive heart failure and persistent fever, the patient was transferred to The Mount Sinai Hospital. Rectal temperature on admission was 102.4°F, pulse, 124/min and respiration, 36/min. The patient was in acute respiratory distress and the liver was palpable 17 cm below the right costal margin in the mid-clavicular line. Chest X-ray showed infiltrates in the right middle and upper lobes and a markedly enlarged heart. The hemoglobin was 8 Gm/100 ml; white blood cell count, 5,850/mm^3 with 83% neutrophils and 10% band forms; BUN, 62 mg/100 ml; ASLO, 1200; and cold agglutinin titer, 1:160. Urinalysis revealed 20 red blood cells per high power field, and 2+ proteinuria. Gram stain of a sputum smear showed few neutrophils per high power field. The patient was begun on 4 gm erythromycin and 4 gm chloramphenicol intravenously per day. LE preparations and the latex fixation test were negative. The patient's congestive heart failure became increasingly severe, his dyspnea increased, and he expired suddenly. The mycoplasma complement fixation titer of serum collected January 28, 1971 was 1:32; the titer 9 days later was >1:256. Serologic tests on paired sera tested for adenoviruses and parainfluenza viruses 1–3 were negative.

Autopsy examination showed rheumatic heart disease with aortic and mitral stenosis and biventricular hypertrophy. There was hemorrhagic pneumonia of the right lung and marked diffuse interstitial pneumonitis. Hyaline-like membranes were evident throughout the lungs and severe bronchiolitis obliterans was present.

Patient 3. A 39-year-old Jamaican female was admitted to The Mount Sinai Hospital with complaints of fever, arthralgia and myalgia for 7 days. The patient was well until one week prior to admission when she developed a diffuse macular erythematous rash followed by shaking chills and fever the same evening. The next morning the patient noted pain in both shoulders which progressed to generalized myalgia. Fever persisted, spiking to 103°F. She visited a physician who prescribed propoxyphene hydrochloride and antihistamines. The next day, she started on steroid therapy. The day of admission, the patient visited another physician who gave her an injection.

On admission her rectal temperature was 102.2°F, pulse 120/min and regular, and blood pressure 120/80 mmHg. A diffuse macular erythematous nonpruritic rash was distributed over the forearms, thorax, abdomen, and face. Laboratory data included a Hgb of 13.2 Gm/100 ml; hematocrit, 41% white blood cell count, 9,500/mm^3 with 80% neutrophils, 8% band forms, 9% lymphocytes and 3% monocytes; reticulocyte count, 1.8%; ESR, 117 mm/hr. Urinalysis on admission showed a pH of 5, 2+ albumin and seven red blood cells per high power field. Serum electrolytes, BUN, creatinine, calcium, phosphorus, bilirubin, and uric acid were normal. The serum, cholesterol was 225 mg/100 ml; total protein 8.5 Gm/100 ml with albumin 3.6 Gm/100 ml; LDH, 345 international μunits; SGOT, 70; SGPT, 55; and prothrombin time (patient/control) 15/12 seconds. LE preparations, antinuclear antibody tests and blood cultures were negative. The patient remained febrile with spikes to 103° and 104°F. She was treated with aspirin and propoxyphene hydrochloride and the rash faded. A bone marrow aspiration performed 4 days after admission was normal. The patient became agitated, developed tremors, and on the sixth hospital day was found to be disoriented and incoherent. Spinal puncture performed at this time yielded clear acellular fluid under normal pressure and with normal glucose and protein concentrations. Brain scan, IVP, skull films, and chest x-ray were negative. On the seventh hospital day, 12 gm of ampicillin daily was instituted. On the eighth hospital day the patient underwent skin and muscle biopsy, taken from the left gastrocnemius, which was normal on histologic exam. The SGOT was 140 and SGPT, 160; liver biopsy was performed and the pathology reported as highly suspicious of lymphoma, probably Hodgkin's disease. Ampicillin was discontinued on the 11th hospital day. Lumbar puncture the next day revealed an opening pressure of 60 mmH_2O; 4 white blood cells/mm^3, 150 fresh red blood cells/mm^3; protein 200 mg/100 ml; and glucose, 243 mg/100 ml. Quantitative serum protein immunoelectrophoresis study showed IgG, 1600 mg, IgA, 240 mg and IgM, 220 mg/100 ml. The mycoplasma complement fixation titer rose from 1:64 to 1:128. On the 13th hospital day, the patient developed a grand mal seizure. Following this, respiration became rapid, then shallow. Electrocardiogram showed atrial fibrillation followed by ventricular fibrillation and attempts at resuscitation were unsuccessful.

Autopsy examination showed bilateral serofibrinous pleural fluid and severe pulmonary congestion. Reticuloendothelial hyperplasia was noted in the spleen and the liver revealed numerous nondiagnostic granulomata. The cause of death could not be determined.

The following viral serologic studies were performed with negative results: influenza A and B, parainfluenza 1–3, adenovirus, psittacosis-lymphogranuloma group, lymphocytic choriomeningitis, mumps, toxoplasmosis, Eastern, Western and St. Louis encephalitides, Rocky Mountain spotted fever, Herpes hominis, Proteus OX19 and OX2. Complement fixation titers for coxsackie B_2-B_6 were 1:16; titers for coxsackie B_1 were, however, 1:512 in two specimens. Attempts at viral isolations from tissue specimens obtained at autopsy yielded negative results.

Comments

Severe pulmonary insufficiency is uncommon with infection due to Mycoplasma pneumoniae. Most patients are in the second and third decades, mainly college students or military recruits, and experience a benign course (14). Patients 1 and 2 had marked pulmonary insufficiency. Lung biopsies and postmortem examinations revealed diffuse interstitial pneumonitis in patient 1 and focal hemorrhage with interstitial pneumonitis and bronchiolitis obliterans in patient 2. These findings are compatible with published reports of interstitial inflammation in primary atypical pneumonia and in M. pneumoniae infections (13, 15). The pulmonary pathology in these reports included interstitial pneumonia, acute bronchiolitis, thickening of the bronchiolar wall with edema, and vascular congestion with mononuclear and plasma cell infiltration. Extensive bacterial and viral cultures and serologic investigations failed to determine another etiologic agent. Patient 1 showed a rise in the mycoplasma complement fixation titer from negative to 1:32. Postmortem culture of the lung yielded Herpes hominis type 1. However, the significance of postmortem cultures remains to be elucidated. Bacteriologic postmortem studies have been unreliable (16). Patient 2 had marked involvement of the right lung with hemoptysis. Hemoptysis has been reported in about 5% of cases of M. pneumoniae infection (17). Overwhelming pulmonary infection with severe rheumatic involvement of the mitral and aortic valves and marked cardiac hypertrophy led to the death of this patient. The mycoplasma complement fixation titer rose from 1:32 to $> 1:256$. A cold agglutinin titer of 1:160 was also noted. A high ASLO titer suggested recent streptococcal infection; however, postmortem examination failed to reveal evidence of acute rheumatic activity. There was severe involvement of the right lung with focal hemorrhages and hemorrhagic involvement of the epithelial lining of the trachea and bronchi. It is interesting to note that this patient had been treated with penicillin and streptomycin at the referring hospital. Although penicillin is without effect, streptomycin is highly active against Mycoplasma pneumoniae (17). Later the patient was given erythromycin which also is highly active against M. pneumoniae (18) but no salutary clinical effect was apparent. Perhaps the infection in this patient with rheumatic heart disease was too overwhelming for these agents to be effective. In patient 3 fever was followed soon thereafter by central nervous system signs. Serologic studies revealed a rise in mycoplasma complement fixation titers from 1:64 to 1:128. Although not diagnostic, we have not found titers of this magnitude to be common in patients without evidence of M. pneumoniae infections. The clinical picture of Patient 3 resembled that of the cases of meningoencephalitis described by Taylor et al (10). In those cases only one patient had an elevated mycoplasm a complement fixation titer. The less specific cold agglutinin titer was elevated in two cases. A 25% mortality has been described in patients with central nervous system complications of primary atypical pneumonia (19).

While there is no doubt that patients 1 and 2 had M. pneumoniae infections the causal role of these infections in their fatal illnesses is suggestive but not proved; no other etiology was determined. Mycoplasma pneumoniae infections may be more virulent in patients with heart disease such as Patient 2. Influenza pneumonia is known to lead to more fatalities in patients with congestive heart failure (20). Patient 3 had elevated complement fixation titers to both M. pneumoniae and coxsackie B_1. Either infection alone or both in concert could account for her illness.

Serologic investigation for possible mycoplasma infection should be determined, not only in patients with unexplained pulmonary infections, but also in those with obscure febrile illnesses so that the pathogenic spectrum of M. pneumoniae may be further elucidated.

Summary

Three patients are presented who died with evidence of infection due to Mycoplasma pneumoniae. Respiratory distress dominated the clinical picture in two patients who had greater than four-fold rises in M. pneumoniae complement fixation titers. Postmortem examinations showed interstitial pulmonary infiltrates consistent with the lung pathology described in primary atypical pneumonia. The third patient had meningoencephalitis and elevated mycoplasma complement fixation titers. The literature dealing with mortality of the usually benign M. pneumoniae infection is discussed.

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Transient Erythrocytosis and Inappropriate Antidiuretic Hormone Secretion in a Patient with Tuberculous Meningitis

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The patient described in this report was admitted to the hospital with acute tuberculous meningitis. He represents a presumably rare example of transient erythrocytosis resulting from acute reversible central nervous system disease, coexisting with another probable indication of altered brain function—inappropriate antidiuretic hormone production.

Secondary erythrocytosis is a well-defined syndrome characterized by an absolute increase in the red blood cell mass which may result from chronic hypoxia, certain types of renal disease, or several different neoplasms (1, 2), and which resolves when and if the primary process is removed. Although there are casual allusions in the literature to the concurrence of tuberculosis and polycythemia (3, 4), it has been felt that these represented coincidental findings. A rare clinical entity has been reported of erythrocytosis in certain patients with disseminated hematogenous tuberculosis in whom, unlike our patient, the spleen has been massively enlarged by the growth within it of many confluent tubercles (5). There are no previous reports of cases of erythrocytosis clearing upon successful treatment of the tuberculosis.

Inappropriate antidiuretic hormone secretion has been well described in patients with tuberculous meningitis and pulmonary tuberculosis (6–9).

Case Report

C.S., a 34-year-old Negro man, was admitted to the tuberculosis service with a chief complaint of headache and dizziness. He first noticed a cough and blood-streaked sputum one year prior to admission, but chest x-ray film taken by a mobile unit was reported as negative. The cough continued, and 2 weeks prior to admission he again noticed occasional hemoptysis. One week later he began to experience shaking chills, fever, and temporal headaches, at first relieved by aspirin. On the day of admission he felt dizzy and came to the emergency room seeking admission. He had a history of a 15-pound weight loss in the last year. He denied a history of tuberculosis and his only known tuberculous contact was his mother whom he last saw in 1952, 14 years earlier. The patient smoked 3 packages of cigarettes a week and drank up to a pint of whiskey daily. He denied a history of liver or kidney disease, high blood pressure, diabetes, or delirium tremors. His maternal grandmother died at the age of 65 with diabetes and hypertension. The remainder of the history was noncontributory.

Physical examination revealed the patient to be a thin, lethargic, Negro man in minimal distress. The blood pressure was 180/120, pulse 80/minute, respirations 28/minute and the temperature 102.2 degrees F. Examination of the lungs revealed dullness to percussion and bronchial breath sounds over the posterior segment of the right upper lobe. His liver

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was palpable just below the right costal margin, and was smooth and nontender. No stigmata of cirrhosis were present. There was no palpable spleen. Neurologic examination revealed him to be oriented, with nuchal rigidity and positive Brudzinski's and Kernig's signs. He had a slight lateral nystagmus and no tremor, but was unable to tandem walk. He had decreased vibratory sensation in his feet as well as dysesthesias of the soles. The remainder of the examination was within normal limits.

On admission his hematocrit was 56%, hemoglobin 16.3 gm per 100 ml, sedimentation rate 5 mm in one hour, and a white blood cell count of 6,500 cells per cu mm. Examination of the urine revealed no albumin or glucose, a specific gravity of 1.025, and no red or white blood cells or casts were noted on microscopic examination of the sediment. Blood chemistry results were as follows: urea nitrogen 11 mg per 100 ml, glucose 120 mg per 100 ml, sodium 112 mEq/L, potassium 4.2 mEq/L, chlorides 87 mEq/L, and carbon dioxide content 22 mEq/L. The electrocardiogram was within normal limits. His chest x-ray film was interpreted as showing moderately advanced pulmonary tuberculosis in the right upper lobe with a cavity. Skull films were normal. Lumbar puncture revealed an opening pressure of 34 cm of water, slight xanthochromia, 243 fresh red blood cells per cu mm, and 162 white blood cells per cu mm. The differential smear of the cells in the sediment showed 44 polymorphonuclear leukocytes, 54 lymphocytes, and 2 monocytes. The spinal fluid glucose was 40 mg per 100 ml with a simultaneous blood sugar of 120 mg per 100 ml, and the protein was 90 mg per 100 ml. Later laboratory results included a culture of the spinal fluid which grew out four colonies of Mycobacterium tuberculosis, with culture for common bacterial pathogens and fungi remaining negative. Sputum cultures were also positive for Mycobacterium tuberculosis. Repeated urine cultures were negative for acid fast bacilli. Blood chemistries including bilirubin, calcium, phosphorous, alkaline phosphatase, cephalin flocculation, thymol turbidity, cholesterol, lactic dehydrogenase, serum glutamic oxalacetic, and pyruvic transaminases were all normal. The protein electrophoresis revealed a total protein of 6.7 gm per 100 ml with an albumin of 2.7 gm per 100 ml. There were no abnormal globulins. Creatinine and uric acid were not elevated on multiple determinations. Stool examinations for occult blood were repeatedly negative. Serologic test for syphilis was nonreactive and hemoglobin electrophoresis revealed only normal A hemoglobin. Intravenous pyelogram was normal. Pulmonary function studies showed a vital capacity of 2.9 liters (70 percent of predicted normal), with a maximum mid-expiratory flow rate of 3.6 liters per second (normal 2–5). Arterial oxygen saturation was 94.8 percent (normal 94–98 percent) and the arterial P_{CO_2} was 43.0 mm of mercury (normal 40 ± 4 mm Hg.).

After completion of the initial examination and lumbar puncture, the diagnosis was presumed to be pulmonary and meningeal tuberculosis, and treatment was started with isoniazid, para-amino salicylic acid and streptomycin. He was initially noted to have a marked hyponatremia. Figure 1 illustrates the changes in the blood, urine, and weight that were presumed to represent the characteristics of transient inappropriate antidiuretic hormone production. Several hours after admission the initial blood specimen was reported to contain a serum sodium of 112 mEq/L, and additional samples of blood and urine were promptly collected. These revealed a serum osmolality of 262 mOsm per kg, and a urine osmolality of 636 mOsm per kg. The urine sodium concentration was 170 mEq/L, indicating significant urine sodium loss in the face of hyponatremia. The hyponatremia gradually corrected itself on a regular oral diet and by the fourth day the serum sodium had risen to 130 mEq/L, the serum osmolality to 294 mOsm per kg and the blood urea nitrogen had risen from 11 to 25 mg per 100 ml. A weight loss of 10 pounds took place in the first 4 days of hospitalization, with an additional 10 pounds lost during the next 6 days.

Of great interest was the presence on and after admission of a definite and marked erythrocytosis. The first 4 hematocrits obtained in the initial 4 days of hospitalization were 56, 53, 55 and 55%. This was quite unexpected for two reasons. First, patients with disseminated tuberculosis are usually anemic. Second, the high hematocrits were noted during a period of endogenous hemodilution, as judged by the low serum sodium values, and due to inappropriate antidiuretic hormone secretion.

The white blood cell counts were normal during this first 4-day period, as were the platelet counts. Persistent temperature elevations, increasing headaches and nuchal rigidity were present, and on the fourth day after admission he was started on prednisone orally in a dosage of 60 mg daily. The temperature rapidly returned to normal and the meningeal signs cleared. Figure 1 indicates the evolution of the hematologic abnormalities. By the tenth day his weight had decreased by 20 pounds and his hematocrit had risen to 61.5%. The hemoglobin also rose from 16.3 to 19.6 gms % during this period. The platelet count remained normal and under 325,000 per cu mm throughout his hospital course. The white blood cell count also rose, due presumably to the high dosage of administered steroids, reaching a maximum of 21,900 cells per cu mm. During this period, the reticulocyte count was 1% and the uric acid and creatinine remained normal. The leukocyte alkaline phosphatase was not elevated.

On the tenth hospital day, when the hematocrit was 59%, a blood volume determination was done using albumin tagged with T-1824 dye. After using a body hematocrit correction of 0.91, the patient was found to have a red blood cell volume of 3275 cc or 60 cc/kg, the normal being 30 cc/kg. At the same time he had a plasma volume of 2824 cc, or 54 cc/kg, which was only a small increase over the expected normal of 45 cc/kg (13).

While receiving prednisone therapy the patient developed diabetes mellitus and hyper-

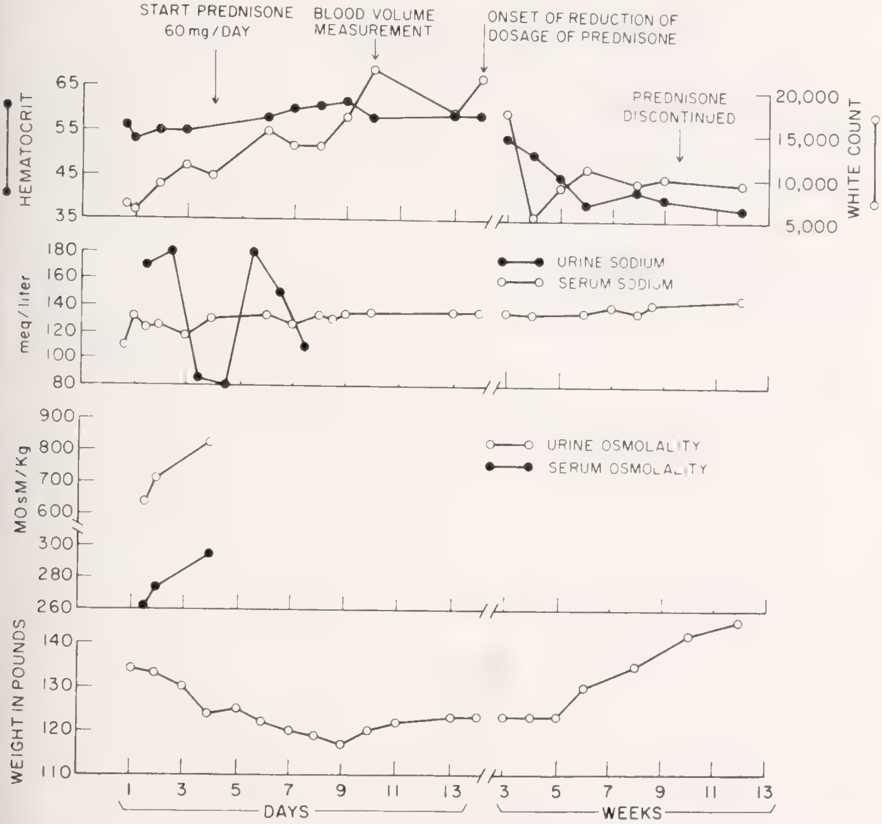

FIG. 1. The chart illustrates the important clinical and laboratory observations noted in this patient from his hospital admission until the disease stabilized.

tension, and two weeks after admission the steroid dosage was tapered and subsequently it was discontinued. His elevated blood sugar and hypertension then cleared and have remained normal on follow-up one and one-half years later. The white blood cell count also returned to normal as the steroid therapy was being tapered. His hematocrit, which had been elevated on each of the four days prior to the onset of steroid therapy, fell to a normal level (38–42%) two months after admission.

The pulmonary and meningeal tuberculosis responded well to treatment. Repeated lumbar punctures showed progressive improvement with normal spinal fluid findings in 2 weeks. The right upper lobe cavity closed slowly and the surrounding densities also resolved. At the time of his discharge, six months after his admission, his sputum was negative on culture. A year and one-half later, still on drugs, the sputum remained negative, the chest x-ray was unchanged, and his hematocrit was stable at 44%, with a white blood cell count of 5,150 cells per cu mm.

The patient returned to Bronx Municipal Hospital Center again in 1970 with a relapse of his pulmonary tuberculosis, due, presumably, to inadequate self-administration of his anti-tuberculous drug therapy. No evidence of tuberculous meningitis was found, however. The hematocrit and serum sodium at that time were normal.

Discussion

The salient features of excess antidiurectic hormone secretion as outlined by Schwartz et al (8) and Goldberg (9) are: 1) hyponatremia and hypotonicity of the body fluids with normal renal function, and urine hypertonicity greater than that of plasma; 2) increased excretion of sodium in the urine despite hyponatremia; 3) normal adrenal function; 4) the absence of dehydration as reflected in a rise of the blood urea nitrogen; 5) absence of edema; and finally 6) the rise of the serum sodium to normal with fluid deprivation. In this case all but the last criteria were satisfied. As the hyponatremia was both asymptomatic and of brief duration, fluid restriction was not specifically stressed. It should be noted that the body electrolyte equilibrium had returned to normal prior to the institution of steroid therapy. This fact coupled with the absence on admission of hyperkalemia and azotemia, and the patient's subsequent well-being during one and one-half years of follow-up without steroid therapy, makes Addison's Disease an unlikely cause of the patient's hyponatremia.

Secondary erythrocytosis is a well-described entity (1, 2) in which there is an absolute increase in the red cell mass to abnormally high levels, no change in the platelet or white blood cell counts, no palpable spleen, and a return of the hematologic abnormalities to normal when the primary process, such as a renal or cerebellar tumor, can be found and removed. In this case the true magnitude of the erythrocytosis was presumably masked initially by the excess water retention due to the inappropriate antidiuretic hormone secretion. When this process cleared, the elevated red blood cell mass became even more evident. Coincident with the successful treatment of the tuberculosis, the erythrocytosis disappeared, leaving a normal hematocrit.

The etiology of the red blood cell abnormality is unclear in this case. None of the well-known causes of transient erythrocytosis existed in this patient. Despite the propensity for polycythemia in Cushing's Disease, long-term studies of persons on high dosage of steroids (9, 10) have not indicated the development of any discernible increase in red blood cell mass.

In review of the hematologic changes in tuberculosis (3, 4) occasional cases of tuberculosis and polycythemia are described. The authors reporting those cases, however, feel that they probably represent the coincidental occurrence of tuberculosis and polycythemia vera. Fitzpatrick and Schwartz (5) in 1949 reviewed the rare but interesting association of massive tuberculous involvement of the spleen and erythrocytosis. Of the 22 cases of definite tuberculosis included in their series, nine probably had true erythrocytosis, as their red blood cell count was over seven million per cu mm. In seven of the nine cases, evidence of disseminated hematogenous tuberculosis was noted either during life or at postmortem examination. The striking feature of these cases was the splenic enlargement in all of them, with the spleen weighing as much as 2250 gms in one of the patients. Splenectomy was required in three of the nine. The surgical and autopsy specimens always showed the spleen to be enlarged due to extensive confluent granulomatous involvement. Unfortunately, no hematocrits, red blood cell masses, or indices of dehydration were mentioned. In three of the nine a significant leukocytosis was also present. No platelet count was noted and little follow-up information was given on these patients. In patients surviving splenectomy, no significant improvement of the erythrocytosis occurred. Because of the lack of data, polycythemia vera or dehydration causing a relative erythrocytosis cannot be excluded. The actual relationship of the tuberculosis to the erythrocytosis is problematical.

The only previous occurrence in the literature of inappropriate antidiuretic hormone production and secondary erythrocytosis was reported in a clinicopathologic conference from Washington University (11). The abnormalities existed in a patient with both a cerebellar hemangioblastoma and ocular lymphosarcoma. In that patient the increased red blood cell mass was easily explained by the established relationship of cerebellar hemangioblastomas and erythrocytosis, and the inappropriate antidiuretic hormone secretion reflected the extensive intracranial disease.

A relationship between erythrocytosis and meningitis has not previously been described. A review of all cases of tuberculous meningitis hospitalized at this institution revealed no other case with erythrocytosis. However, a definite but infrequent role of central nervous system disease in the etiology of erythrocytosis is suggested by the report of Gilbert and Silverstein (12), on "neurogenic polycythemia." Their patient was hospitalized as a result of a middle cerebral artery occlusion. A documented increase in red blood cell mass was noted, which disappeared as the neurological disease improved. Careful studies revealed no apparent cause for the erythrocytosis. The authors comprehensively reviewed the clinical and experimental data suggesting a cause and effect relationship between instances of central nervous system disease and the erythrocytosis observed in the affected patients.

Although we cannot, with absolute certainty, delineate a clear etiologic relationship of the meningitis to the erythrocytosis in our patient, we feel that the simultaneous occurrence and resolution of the tuberculosis and the erythrocytosis, coupled with an absence of any other cause for the red cell abnormality, suggest that it was the result of the acute central nervous system disease.

Conclusion

A patient with tuberculous meningitis is described in whom inappropriate antidiuretic hormone prduction, and true but transient erythrocytosis coexisted. Both processes cleared as the tuberculosis was successfully treated. No similar clinical situation has been documented in the literature. Although no definite pathogenesis for the erythrocytosis was demonstrated, a similarity between this case and a previously described case of "neurogenic polycythemia" is proposed.

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Segmental Portal Hypertension due to Congenital Cavernous Malformation of Splenic Vein

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Splenic vein thrombosis is a well-recognized entity. Initially reported at autopsy examinations in 1922 (1), its diagnosis during life has been elusive until the introduction of methods of radiographic visualization of the portal venous system. The case reported here illustrates the clinical and laboratory features of this condition.

Case Report

G.K., a 28-year-old Negro woman, mother of four children, was admitted to The Mount Sinai Hospital with recurrent hematemesis and melena. She had previously consumed alcohol heavily, but had allegedly abstained for two to three years prior to the current admission. In August 1967, during the second trimester of her second pregnancy she experienced an episode of hematemesis and melena for which she was hospitalized. The bleeding ceased spontaneously shortly after admission, and no blood transfusion was given. Endoscopic examination of the esophagus and stomach were reportedly normal. Radiologic studies of the gastrointestinal tract were postponed until after childbirth. Physical examination and laboratory investigations revealed no abnormality; the patient was discharged and delivered a normal baby. She was readmitted several months later with severe upper gastrointestinal bleeding. Apart from a hematocrit of 21% no clinical or laboratory abnormality was found. Blood transfusion (7 units) was instituted and the patient's condition stabilized. Esophagogastroscopy revealed no abnormality, but a small duodenal polyp was found on upper GI series. Laparotomy was performed. No abnormality other than the duodenal polyp was found and a polypectomy was carried out. She made a successful postoperative recovery, but less than a year later, in December 1968, she was again hospitalised for upper gastrointestinal bleeding during her third pregnancy. Complete blood coagulation studies were normal. Gastroscopy and barium studies of the gastrointestinal tract were unremarkable. The bleeding stopped spontaneously and she delivered a normal child. In August 1969, during the eighth month of her fourth pregnancy, she experienced the fourth episode of major upper gastrointestinal bleeding. Following blood transfusion, the bleeding stopped. She remained hospitalized until after childbirth. Gastrointestinal radiology and endoscopy were again normal. Tubal ligation was performed a few weeks after childbirth. Two months later, in November 1969, she was once more readmitted with massive upper gastrointestinal bleeding. She was hypotensive with a blood pressure of 70/40 and a pulse rate of 140/min. For the first time splenomegaly was noted 5 cm below the left costal margin.

Laboratory Investigations. Hemoglobin 8.3gm%, WBC 5,100 with a normal differential count. Sedimentation rate 19 mm/hr, BUN 21mg%, Glucose 115mg%, CO_2 25.5mEq/L, Cl 106 mEq/L, Na 162 mEq/L, K 4.8 mEq/L, amylase 20 Somogyi units/L. Platelet count was 202,000; the prothrombin time, serum iron, iron binding capacity, alkaline phosphatase, SGOT, LDH, cholesterol and proteins were within normal limits. Urinalysis was normal. Chest x-ray and EKG showed no abnormality.

Because of the repeatedly normal endoscopy and upper GI series on previous admissions, selective angiography was carried out as the first diagnostic procedure. Through a cathe-

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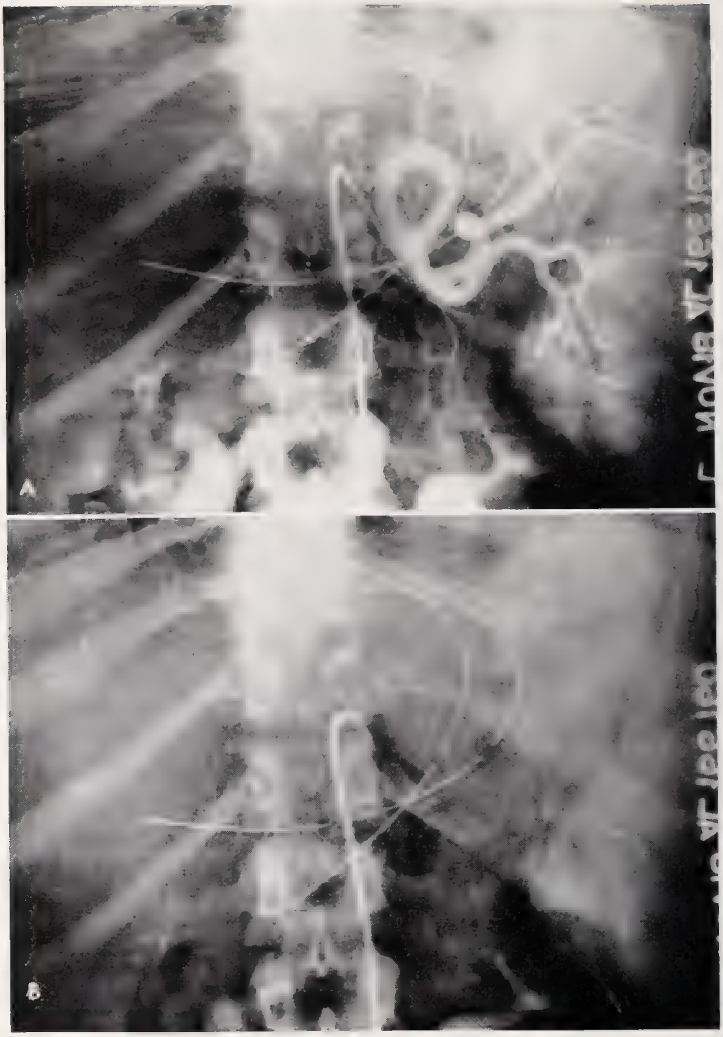

FIG. 1. Selective splenic angiography. (a) Arterial phase. (b) Venous phase.

ter in the femoral artery the splenic artery was cannulated and the dye injected. The arterial phase (Fig. 1a) demonstrated an enlarged spleen but no abnormal vasculature. The venous phase (Fig. 1b) failed to demonstrate a normal splenic or portal vein. This was followed by superior mesenteric ateriography. The arterial phase (Fig. 2a) revealed a normal arterial tree. In the venous phase (Fig. 2b) normal drainage of the superior mesenteric vein into the portal vein was noted. The combination of a normal venous drainage into the portal system with superior mesenteric artery injection and failure of opacification of the splenic vein and portal vein with a celiac artery injection was strong evidence that the etiology of the bleeding was varices due to splenic vein thrombosis. This was further confirmed by splenoportography (Fig. 3); the splenic vein was not seen and multiple venous collaterals and varices were noted. Splenic pulp pressure was markedly elevated—57.0 cm water.

Operation. A preoperative diagnosis of gastric and esophageal varices due to segmental

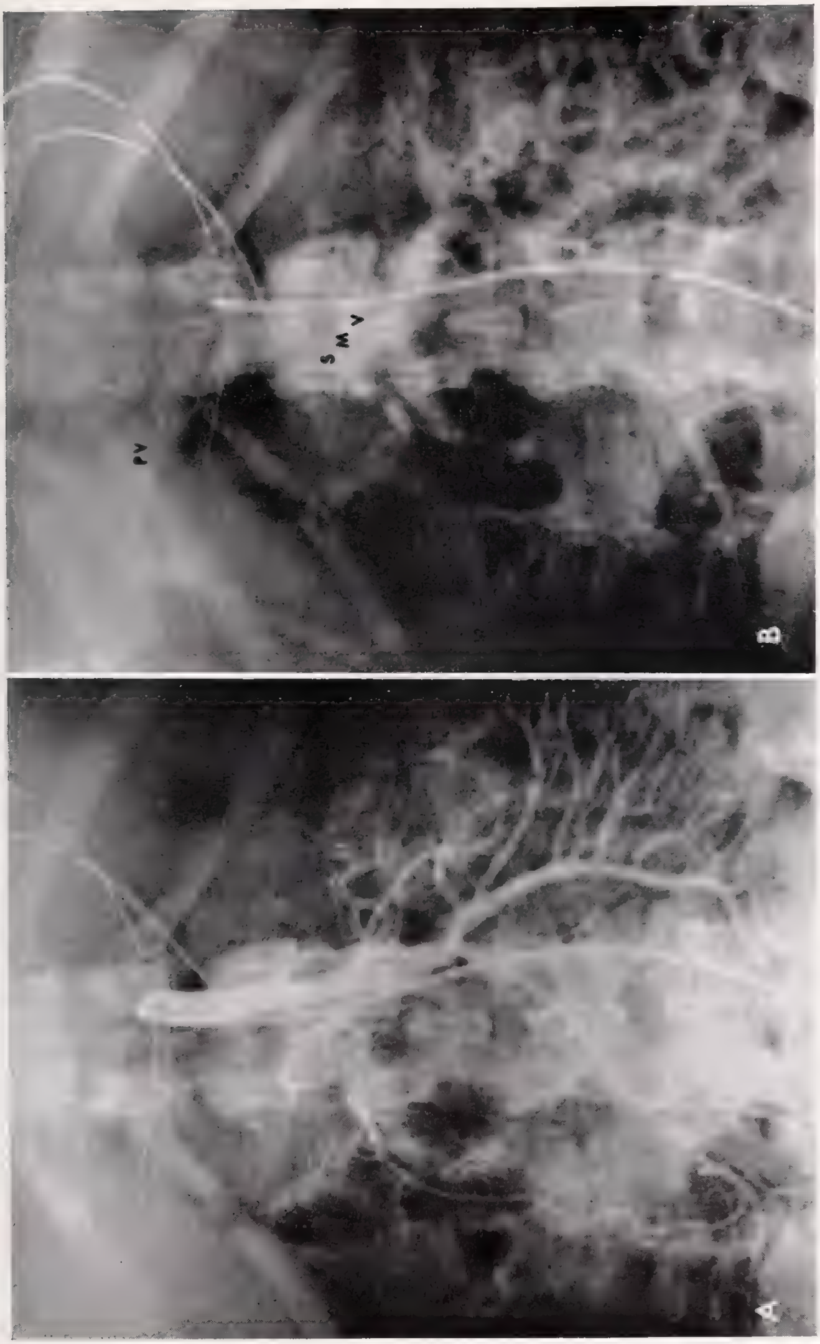

FIG. 2. Selective superior mesenteric angiography. (a) Arterial phase. (b) Venous phase.

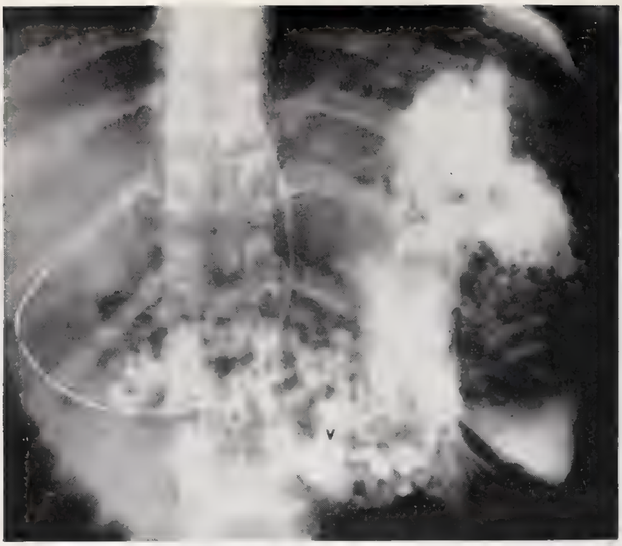

FIG. 3. Splenoportogram demonstrating varices (V).

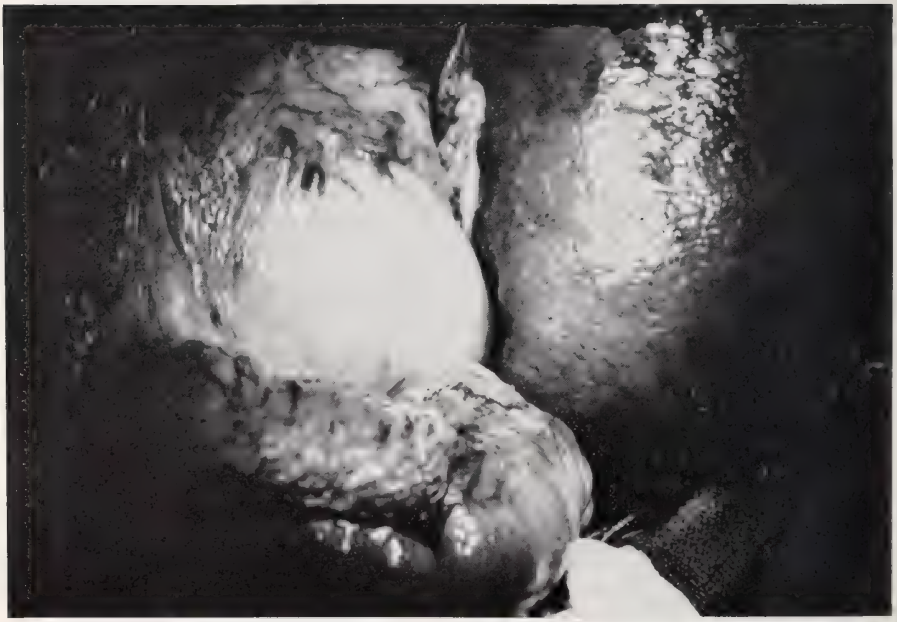

FIG. 4. Large varices in the wall of the stomach.

portal hypertension resulting from splenic vein thrombosis was made. At laparotomy, the spleen was enlarged but the liver was macroscopically normal. Pressure in a short gastric vein was 56.0 cm water but the pressure in the portal vein was 15.0 cm water. Numerous thick varices were noted in the wall of the stomach (Fig. 4), occupying a wedge-shaped area with the base of the wedge along the greater curvature and the apex at the lesser curvature of the stomach. A large varix, 4 cm diameter, was palpable through the wall of

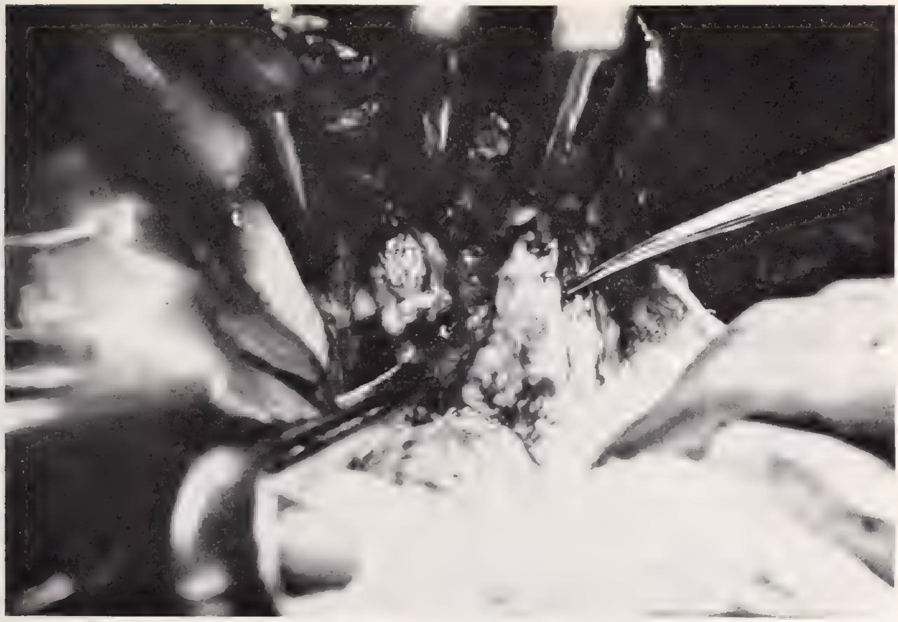

FIG. 5. The firm nodule in the tail of the pancreas.

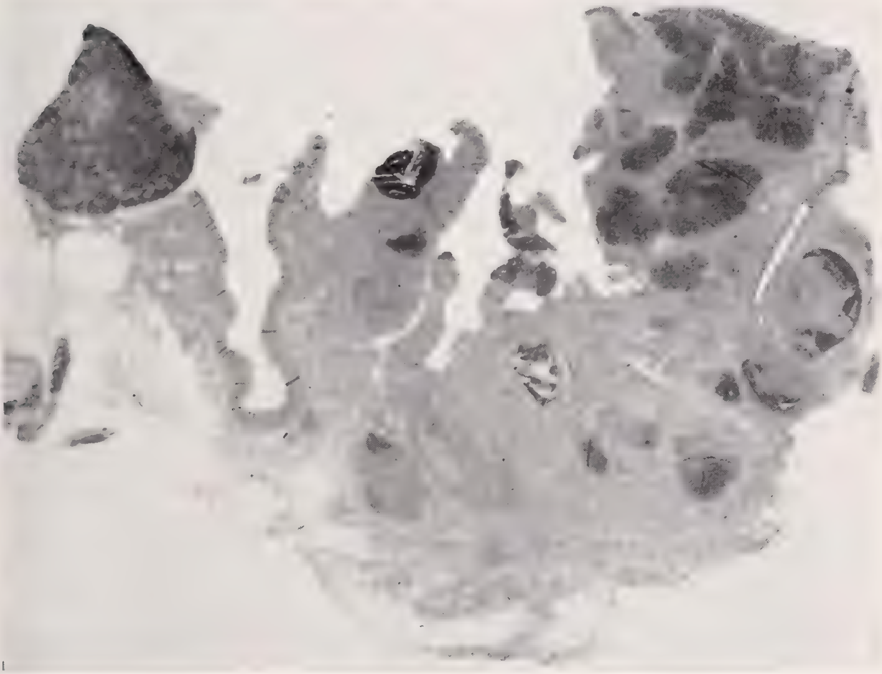

FIG. 6. Microscopic section of pancreas demonstrating thrombosed veins.

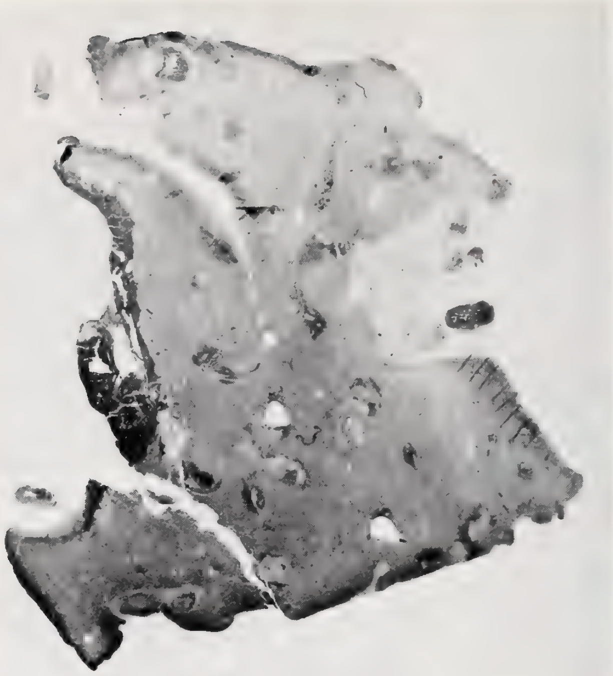

FIG. 7. Cavernous malformation of splenic vein with fibrosis of tail of pancreas.

the stomach protruding into the lumen. No esophageal varices were noted. Further varices and collateral channels were seen retroperitoneally posterior to the lesser sac. The splenic vein was obviously thrombosed. A hard nodule was palpated in the tail of the pancreas (Fig. 5). It was impossible to differentiate macroscopically between a tumor or a localised pancreatitis. Splenectomy and distal pancreatectomy was carried out. Venous thrombi were noted in the cut end of the pancreas.

Pathology. (Figs. 6 and 7). There were cavernous changes in the veins in the spleen, in the splenic vein, and in some pancreatic veins draining into the splenic vein. New and old thrombi were present in these veins. The arteries were normal. The hard nodule in the tail of the pancreas was due to fibrosis—probably secondary to the vascular changes.

Discussion

The incidence of isolated splenic vein thrombosis is very low. In a study of 327 cases of thrombosis in the portal system, Grunert (2) found isolated splenic vein thrombosis to occur in only 1.2 percent whereas isolated portal vein thrombosis occurred in 32.7 percent of cases; combined thrombosis involving the portal, splenic and mesenteric veins accounted for 33.4 percent of cases. The thrombosis may involve varying lengths of the splenic vein ranging from a very short segment to half the length of the vein; the length of the thrombosed segment does not necessarily correlate with the symptomatology (3).

Numerous causes of splenic vein thrombosis have been described: carcinoma of the pancreas, carcinoma of the stomach, recurrent cholecystitis, acute pancreatitis, carcinoma of colon, renal carcinoma, trauma, myeloproliferative disorders and polycythemia vera (3–6). To this list must now be added cavernous malformation of the splenic vein. Although we have assumed this to be congenital in our patient, the etiology may be inflammatory. Shaldon and Sherlock (7) have reported splenic vein thrombosis in childhood secondary to omphalitis. conceivably, a similar mechanism might have accounted for the splenic vein thrombosis in our patient, despite her age.

The mode of presentation of splenic vein thrombosis is variable. Ranging from the asymptomatic patient diagnosed incidentally on x-ray, it may present as massive hematemesis at the other end of the spectrum. Splenomegaly, although not always present, is frequent; on occasion a coexistent blood dyscrasia may account for the splenic enlargement. A common feature is the segmental portal hypertension presenting as upper gastrointestinal bleeding. Splenic pulp pressure in our patient was 57.0 cm water whereas portal venous pressure was only 15.0 cm water. A wedge-shaped area (with the base of the wedge on the greater curvature) of the stomach was involved in variceal formation. Collateral circulation to the portal vein had occurred in our patient, mainly via the gastric and gastroepiploic veins. Although retroperitoneal varices were also present, no varices were present in the lower esophagus.

The chief interest of this case is the demonstration of the feasibility of diagnosing splenic vein occlusion angiographically. The radiologic features merit consideration. In the normal portal system blood flow is hepatopetal (toward the liver), but in portal hypertension the direction of blood flow, at least in part, is altered and becomes hepatofugal. Blood returns to the systemic venous system along various tributaries and collateral veins away from the liver, and flow in the splenic vein may be reversed. Primary splenic vein occlusion provides an exception to hepatofugal blood flow. With the elevation of splenic pulp pressure with a normal portal vein pressure, the short gastric-gastric-coronary vein route and the gastroepiploic vein route act as bridging collaterals and the blood flow is toward the liver, i.e., hepatopetal. Similar radiologic features would therefore be expected with splenoportography and the venous phase of splenic arteriography. Neither the splenic nor portal vein opacify; contrast medium passes from the spleen toward the liver over bridging collaterals. In sharp contrast, with superior mesenteric arteriography, the venous flow pattern in the superior mesenteric and portal veins is normal.

The "spleen-hilum time," i.e., the time needed for a dye injected into the spleen to appear in the hilum of the liver, has been advocated (8) as a diagnostic procedure. When it exceeds two seconds it is regarded as prolonged, suggestive of splenic vein occlusion.

Once diagnosed, the treatment of splenic vein thrombosis is straightforward. Unlike portal hypertension or portal vein thrombosis, no shunt is necessary. All that is required is a splenectomy. Our patient remains well 2 years after splenectomy and has had regression of the gastric varices with no recurrence of bleeding.

It is noteworthy that our patient bled repeatedly during pregnancies. It is debatable whether this was due to increased pressure during pregnancy or to progesterone-estrogen vascular changes. Pressure changes may have been important since both superior and inferior vena caval hypertension normally occurs in the third trimester of pregnancy. Perhaps this is related to the hypervolemia of pregnancy.

Summary

A case of segmental portal hypertension due to cavernous malformation and thrombosis of the splenic vein is described. Repeated barium and endoscopic studies were repeatedly of no value, but selective arteriography and splenoportography was diagnostic. Splenectomy effected a satisfactory cure. The occurrence of bleeding during separate pregnancies is of interest.

Acknowledgment

We are indebted to Dr. M. Kaneko for his interpretation of the histologic findings.

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The Present Status of Levodopa and Future Approaches to Therapy

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It has been established by many investigators (1–4) that levodopa is the treatment of choice in patients with Parkinson's disease. Two hundred and fory-two cases of Parkinson's disease treated at The Mount Sinai Hospital with levodopa have been analyzed. The status of these patients was evaluated as of January 1, 1971, by which date they had a minimum of one year and a maximum of two years follow-up period. One hundred and eighty-five patients are being followed and are still on L-dopa therapy (Fig. 1). All patients with Parkinson's disease who were seen at the Mount Sinai Hospital were started on L-dopa therapy unless there were medical reasons not to start a new drug. The details and data of these patients have been previously published (5–6).

Of these 185 cases now under treatment, 116 (or 48%) have definitely improved, with a change in their life style noted. Another 35 patients are slightly better with L-dopa therapy and have continued taking the drug. Thirty-four patients have not improved with L-dopa, but neither has their disease progressed. They have, therefore, continued levodopa therapy. Of these 34 patients, 12 definitely became worse when L-dopa was stopped temporarily.

Thirty-seven patients have been lost to follow-up or have stopped the drug for various reasons. Nine moved to different locations and are followed by other physicians. Five were definitely better when last seen. Four patients stopped L-dopa because of other diseases not related to Parkinson's disease or L-dopa therapy. Twenty-four patients had no help from the drug or the complications were so severe that the levodopa was stopped.

Of the original 242 patients started on L-dopa therapy, 20 have died (Fig. 2). Eight of these patients died after having been off the drug for at least one month, and their deaths could not be related to L-dopa therapy in any way. Twelve patients died while on L-dopa therapy, or in a one-month period after the drug was stopped. Of these twelve patients, five died of cardiac complications, two of pulmonary disease, and one of a bleeding cerebral aneurysm which was previously documented. Four patients died at home of unknown causes. In none of these patients was the death clearly related to L-dopa therapy. One patient developed a myocardial infarction while in the hospital on L-dopa therapy. There was never any evidence of hypotension or cardiac arrhythmia brought on by L-dopa, but this death must be considered a possibly related phenomena. A control group of 242 patients with Parkinson's disease in this age group who were not treated with L-dopa is not available to us; however, it is our clinical impression that the deaths were not related in any way to L-dopa.

These data may give some general idea of the way L-dopa has changed the

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		No. of Patients
TOTAL (1-2 year follow-up)		242
Died		20
Stopped drug or not followed		37
Followed on L-Dopa		185
A) Better		116
Almost normal	26	
Regressed		
1. on reduced drug	21	
2. on drug	7	
B) Slightly Better		35
Regressed		
1. on reduced drug	8	
C) Not Better		34
Regressed		
1 on reduced drug	12	

Fig. 1.

PARKINSON'S PATIENTS ON L-DOPA

1-2 year follow-up period as of 1/1/71

Deaths	20
Off drug 1 month	8
On drug in month before death	12
Cardiac	5
Pulmonary	2
Cerebral Aneurysm	1
Unknown (sudden)	4

Fig. 2.

outlook in Parkinson's disease. Approximately 50% of the patients treated do well and have a change in their life style. In a one- or two-year follow-up period, the general response has not changed dramatically; however, it is not known what the long-term follow-up will be. L-dopa has not been of help in patients with severe organic mental syndrome or with severe tremor. Most of the patients who improve with L-dopa still have signs of Parkinson's disease; however, six patients were normal on neurologic examination after L-dopa was instituted and another 14 patients had minimal signs which could be noted only by a neurologic examination. Of the 185 patients who were still taking L-dopa therapy, 41 had their drug temporarily reduced as a trial experiment and, in all of these patients, an increase in the Parkinson syndrome was noted.

Although the figures are impressive when compared to the results with the older drugs, most patients on L-dopa therapy still have symptoms of Parkinson's disease and these symptoms create many disabilities in their daily activities. The following portion of this paper is related to possible future developments and recent experience in this regard at the Mount Sinai Hospital, New York.

Future Approaches to Therapy of Parkinson's Disease

I. The only method of controlling any disease is to stop the disease from occurring. But, unfortunately, the cause of idiopathic Parkinson's disease, which represents 93% of our patients, is not known. Rare cases of poisoning due to manganese or carbon monoxide do occur, but these cases do not represent a large group of patients in this country. Parkinson syndrome due to phenothiazine, reserpine, or haloperidol is reversible when the drugs are removed. Postencephalitic Parkinson's disease represents only about 7% of the total patient population in the United States today and probably is a disappearing disease as the survivors of the 1916 epidemic die. A number of investigators (7) believe that Parkinson's disease is caused by a virus which infects the brain at an early age. However, at this date, there are no agglutination tests or viral culture methods available to prove this hypothesis. No progress has been made to prevent Parkinson's disease in the past ten years.

II. The second approach might be an attempt to diagnose the disease at an early stage so that therapy is started and progression is stopped. There is some evidence from the analysis of patients treated with L-dopa that younger patients with mild disease do better than older patients with more advanced Parkinsonism. There also appears to be a lack of progression in most patients with Parkinson's disease when on L-dopa therapy for one to two years. An objective test, therefore, to diagnose Parkinson's disease at an early stage is important. Many patients in early stages of Parkinson's disease have vague bizarre complaints which are not readily diagnosed until a year or two later.

Recent information that the dopamine level in the basal ganglia in Parkinson's disease patients is reduced has given hope that an objective biochemical test can be developed. The brain is inaccessible to testing; however, the spinal fluid homovanillic acid may reflect the concentration of dopamine in the brain (9). Homovanillic acid has been shown to have lower values in the spinal fluid of Parkinson patients than in normals (10). The determination of homovanillic acid in the spinal fluid, however, is not diagnostic because some patients with other diseases of the nervous system have low homovanillic acid levels in the spinal fluid. In our own data (11) at The Mount Sinai Hospital, we have determined that spinal fluid homovanillic acid level in 120 patients. Only one patient with typical Parkinson's disease had a homovanillic acid level over 20 ng./ml. of spinal fluid. Some non-Parkinson patients, however, have had homovanillic acid concentrations below this level.

Newer methods of studying the spinal fluid homovanillic acid are being developed by the use of probenecid (Fig. 3). Probenecid blocks the uptake of homovanillic acid in the fourth ventricle (12) so that the concentration of ho-

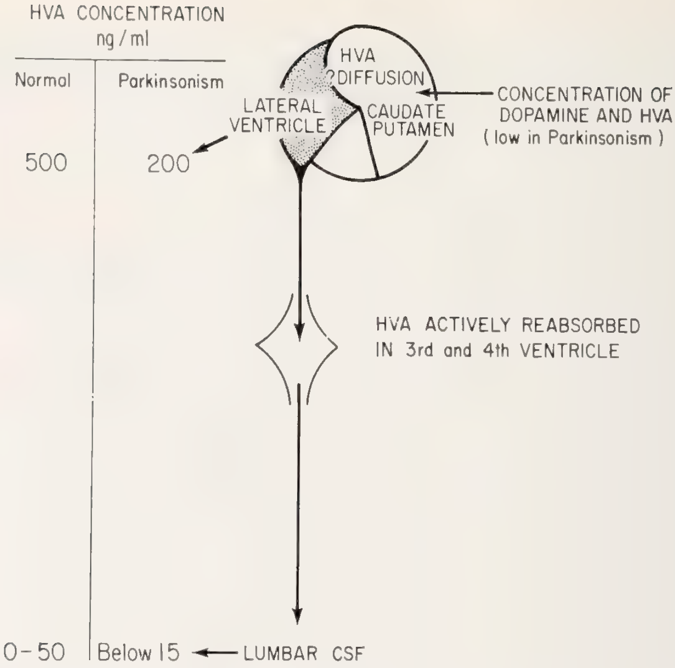
HVA CONCENTRATION
ng / ml
Normal
Parkinsonism
500
200
0-50
Below 15
LATERAL VENTRICLE
HVA ?DIFFUSION
CAUDATE PUTAMEN
CONCENTRATION OF DOPAMINE AND HVA (low in Parkinsonism)
HVA ACTIVELY REABSORBED IN 3rd and 4th VENTRICLE
LUMBAR CSF

Fig. 3. The homovanillic acid in the spinal fluid in the lateral ventricle probably arrives there by passive diffusion thru the ependymal layer of the caudate nucleus. The low concentration of (HVA) in the Parkinson patients mirrors the low concentration of dopamine and HVA in the neostriatum of these patients. The active reabsorption of HVA in the third and fourth ventricles can be blocked by probenecid (See Text).

movanillic acid rises in the spinal fluid when one to two grams of probenecid is given a day. It is hoped that this loading technique may make the spinal fluid determinations more representative of brain dopamine levels and, thus, a more valuable diagnostic test.

III. A number of new pharmacologic approaches to Parkinson's disease are being studied. Dopadecarboxylase inhibitors can stop the breakdown of L-dopa to dopamine in the extracerebral areas of the body (13). It is established that a large percentage of L-dopa given orally is decarboxylated quickly in the blood, GI tract, liver, so that most of the L-dopa given is lost to the brain. Only the L-dopa in the blood crosses the blood-brain barrier and then has the ability to raise the dopamine level in the basal ganglia of the brain, (Fig. 4). Two drugs that inhibit the decarboxylation of L-dopa have been developed. One of these is alpha-methyl-dopa-hydrazine or MK 486 (Merck) which is now under investigation at Mount Sinai Hospital. This drug stops the breakdown of L-dopa to dopamine in the peripheral parts of the body, but does not cross the blood-brain barrier and, therefore, does not change the ability of the brain to decarboxylate L-dopa to dopamine. Approximately 20% of the amount of L-dopa is needed for a clinical response when the enzyme is added to the original amount of L-dopa needed previously. It is not established, however, if the results with the inhibitor and L-dopa together are significantly better than the results with L-dopa alone. Nor is it established that the toxicity seen with L-dopa alone is reduced when the combination of drugs is used.

A group of 16 patients who were relatively unresponsive to L-dopa therapy alone for periods of six to twelve months have been evaluated at the Mount Sinai Hospital with a combination of L-dopa and MK 486. Seven patients had a clinical improvement in status which appeared to be related to the addition

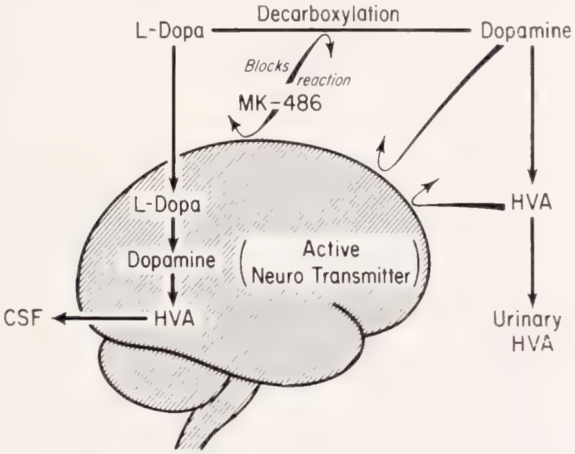
L-Dopa
Decarboxylation
Dopamine
Blocks reaction
MK-486
L-Dopa
Dopamine
Active Neuro Transmitter
CSF
HVA
HVA
Urinary HVA

Fig. 4. Alpha-Methyl-Dopa Hydrazine (MK-486) blocks the decarboxylation of dopa to dopamine in the peripheral tissues. MK 486 does not itself enter the brain and, therefore, the build up of dopamine from dopa in the brain is not impaired.

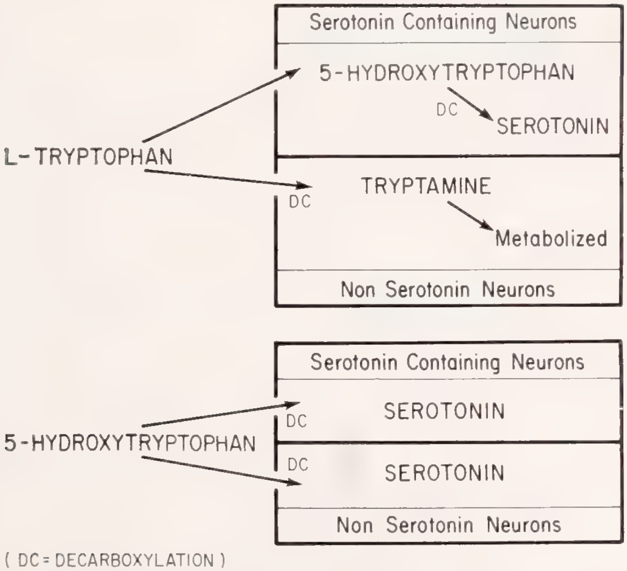
Serotonin Containing Neurons
5-HYDROXYTRYPTOPHAN
DC
SEROTONIN
L-TRYPTOPHAN
TRYPTAMINE
DC
Metabolized
Non Serotonin Neurons
Serotonin Containing Neurons
DC
SEROTONIN
5-HYDROXYTRYPTOPHAN
DC
SEROTONIN
Non Serotonin Neurons
(DC = DECARBOXYLATION)

Fig. 5. Note that 5-Hydroxytryptophan increases serotonin concentration in both serotonin and Nonserotonin neurons. L-tryptophan is changed to serotonin only in neurons normally containing serotonin.

of MK 486 to the therapeutic regime of L-dopa. Six patients were unresponsive to the MK 486 L-dopa combination. Another three patients had toxic phenomena when the MK 486 was added so that there was no improvement in their previous response. The blood levels of L-dopa in these unresponsive cases were high and, thus, the problem in the non-responsive patient does not appear to be related to the absorption of the L-dopa in the GI tract, nor is it related to the increased breakdown of L-dopa in the peripheral parts of the body. More likely, the nonresponsiveness to L-dopa in the Parkinson patients is related to the specific brain mechanisms.

The responsiveness of patients to MK 486/L-dopa combination will be reported at a later date.

IV. Serotonin metabolism. In addition to the decrease in dopamine level in the basal ganglia of Parkinson patients, it has been shown that the serotonin level in these patients is reduced 50% (14). It is not known, however, if this reduction in serotonin has any clinical meaning in the Parkinson patients. L-dopa given orally in large doses reduces the concentration of serotonin in the basal ganglia and, thus, it is possible that the reduction of serotonin in the basal

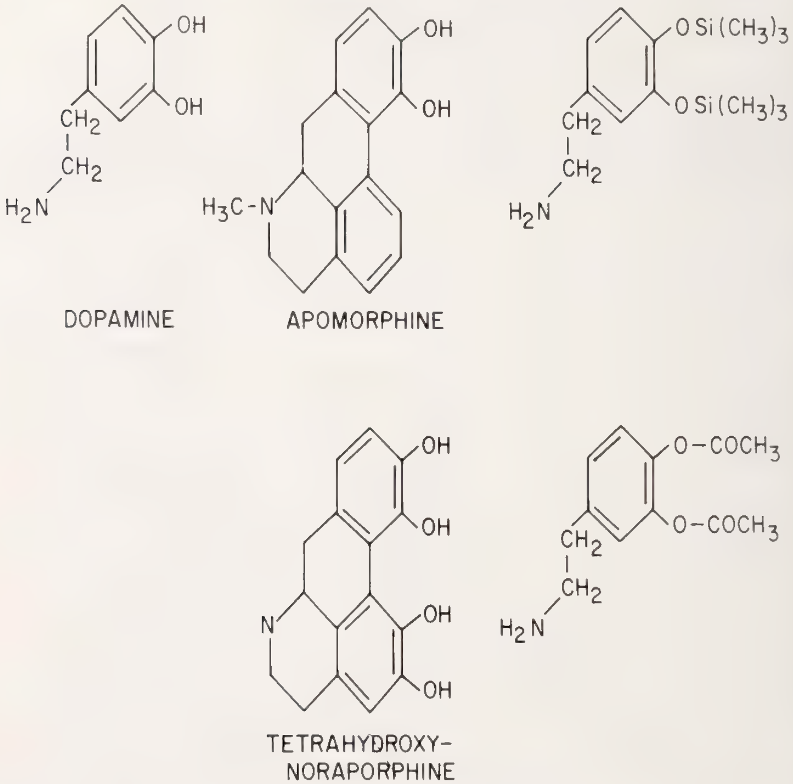

FIG. 6. The similarities of these four chemicals to Dopamine are obvious. Apomorphine has been shown to have an effect on Dopamine receptors. Other derivates are being tested (See Text, References 16–20).

ganglia of Parkinson's disease patients is related in some way to the responsiveness of the patient to L-dopa or to the toxicity of the drug itself. At The Mount Sinai Hospital, six Parkinson patients with L-dopa induced dyskinesias have been given L-5-Hydroxytryptophan in doses as high as 500 mg. per day. No toxicity or improvement has been noted in these patients. Recently, Aghajanian (15) noted that the serotonin containing neurons in the brain are situated only in the mid-brain raphe system. L-5-Hydroxytryptophan given intraperitoneally did not increase the amount of serotonin in these cells alone. Diffuse fluorescence was seen in many parts of the brain which do not normally contain serotonin. Possibly decarboxylation of L-5-Hydroxytryptophan occurred in many areas of the brain which do not normally contain serotonin. Tryptophan, however, may only be hydroxylated in cells containing serotonin and, therefore, may be a better drug to raise the serotonin levels specifically in mid-brain raphe serotonin system, (Fig. 5). Work is now being done treating patients with Parkinson's disease with L-Tryptophan. No data is yet available on this project.

V. Another important approach is the development of a new dopamine-like drug. It has been known since 1945 that apomorphine can improve the symptoms of Parkinson's disease patients (16). Apomorphine has a structure similar to dopamine (Figure 6) and causes gnawing movements and abnormal dyskinesias in animals as does L-dopa. Cotzias showed that apomorphine can improve tremor and other symptoms of Parkinson's disease on a short-term basis (17). This information had led to a search for an artificial drug which stimulates the dopamine receptors, as does apomorphine, but does not have the side effects of the drug. Such drugs are now being developed and tested (17–20), but no practical approach has been achieved in this regard.

Summary

In this series of 242 patients with Parkinson's disease, followed for from one to two years, 50% of the patients are doing well with little toxicity. Another 25% of the patients are not responding well to the drug, and 25% have been lost to follow-up or have stopped the drug completely.

New approaches to the treatment of patients who do not respond well to L-dopa have been discussed. The importance of early diagnosis and treatment with L-dopa is discussed as are new techniques using spinal fluid as a diagnostic method. Dopadecarboxylase inhibitors represent a new advance in the treatment of Parkinsonism; however, it is not yet established what the exact role is that these enzyme inhibitors will play in clinical medicine. Serotonin precursors have been used to treat Parkinson patients, but no definite improvement has been seen with these chemicals alone or with L-dopa. Lastly, artificial dopamine-like drugs are being developed in an attempt to create chemicals which will help Parkinson's disease, but will lack the side effects of L-dopa.

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Relationship between Smoking History and Complications Immediately Following Surgery for Duodenal Ulcer*

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The purpose of this paper is to summarize the analyses regarding the relationship between smoking history and complications immediately following surgery for duodenal ulcer. Analysis included comparisons made involving length of time smoked and number of cigarettes smoked per day with regard to certain types of postoperative complications and number of days to discharge following surgery. Similar comparisons were made involving pipe smokers and cigar smokers.

Investigators from 19 Veterans Administration hospitals participated in a study with the primary purpose of determining which surgical procedure, designed to alter gastric physiology, produces the best results, in the sense of morbidity and mortality, in patients with proven duodenal ulcer disease. As a part of this project, a smoking history was obtained from the patients; however, this aspect of the study was not included in the initial planning so that many patients in the study had no smoking history recorded. Thus, although a total of 2988 patients were in the study, as originally designed, only 1441 patients had a smoking history recorded.

Since Claude Bernard mentioned *le tabac* as influencing gastric secretion there has been much speculation regarding the relationship between smoking and peptic ulcer. Barnett (1) in 1927 summarized the writings to that date and concluded there was no proof that smoking was of any importance in the etiology of peptic ulcer. Trowel (2) in 1934 agreed with this conclusion. In the next two decades there were surveys and epidemiologic studies to show that there was a higher proportion of cigarette smokers among male ulcer patients and also that the effect of smoking was to interfere with the healing of the ulcer (3–8).

There have been few physiologic studies and Packard (8) in 1960 called most of them inconclusive. Schnedorf and Ivy (9) found changes in gastric mobility and secretion with smoking, but rarely to a significant degree. Steigman (10) found an increase in acid production and gastric mobility with cigarette smoking. Cooper and associates (11–15) found no changes in careful studies of the effect of smoking on intragastric balloon pressure and temperature, on gastric secretions, on dissolved gastric mucins, on viscosity of gastric juice, and on excretion of uropepsin and concentration of plasma pepsinogen.

Limitations of the Study

Inasmuch as the study is limited to men entering Veterans Administration Hospitals with duodenal ulcer, one should be careful in making inferences from the results presented herein to the general population. No bias was introduced, no patients were intentionally entered or omitted from the study. Clearly, patients were not randomly selected from the general population and patterns established in the data may not apply in general. In particular, the age and

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TABLE I

Age versus Smoking Habit

Smoking Habit	Age							
	20–29	30–39	40–49	50–59	60–69	70–79	80 and over	Total
Nonsmoker	4	40	68	54	59	47	1	273
Cigarette only	35	233	381	205	117	45	2	1018
Cigar only	0	7	10	4	8	3	0	32
Pipe only	0	0	1	3	6	5	1	16
Cigarette and cigar	0	5	18	11	4	0	0	38
Cigarette and pipe	0	6	10	5	10	3	0	34
Cigar and pipe	1	0	6	2	0	0	0	9
Cigar, cigarette, and pipe	3	4	7	1	3	3	0	21
Total	43	295	501	285	207	106	4	1441

socioeconomic distributions for patients in Veterans Administration Hospitals are not representative, not to mention the all-male selection inherent in the study. The distribution of the 1441 patients by age and smoking habit is given in Table I; clearly, most of the patients were cigarette-only smokers in the 30–69 year age interval.

Analyses

For purposes of analyses, the complications were considered as being of seven types: atelectasis and pneumonia; thrombophlebitis and pulmonary embolus; cardiac complications; urinary tract complications; bleeding; intraabdominal complications; and general systematic complications. Smokers of cigars only, pipe only, or pipes and cigars were not considered with the cigarette smokers. Moreover, classification of patients by age was condensed to those less than 50 years of age and those 50 years or older.

Table II summarizes length of time smoking, age, and type of complication. Of the 110 patients who were nonsmokers and less than 50 years of age: five (4.5%) had atelectasis and pneumonia; three (2.7%) had thrombophlebitis and pulmonary embolism; none had cardiac complications; four (3.6%) had urinary tract complications; two (1.8%) had bleeding; 11 (10.0%) had intraabdominal complications; and one (0.9%) had general systemic complications. Other columns of the table have a similar interpretation.

It should be clear from the table that, within a particular age group, the complication rate is essentially the same for nonsmokers, smokers who have smoked 11–20 years, and smokers who have smoked 21 or more years. In contrast, those who have smoked less than ten years seem to have a more favorable complication rate than other smokers except for the intraabdominal complications in those patients less than 50 years of age. No explanation can be offered for this finding.

The number of cigarettes smoked per day, age, and type of complication are

TABLE II

Length of Time Smoked, Age, Type of Complication

Type of Complication	Nonsmoker		<10 years		11–20 years		21+ years	
	<50	50+	<50	50+	<50	50+	<50	50+
Atelectasis and pneumonia								
Number	5	9	0	0	14	1	19	23
Per cent	(4.5)	(5.6)	(0.0)	(0.0)	(5.2)	(3.6)	(5.0)	(6.3)
No atelectasis and pneumonia								
Number	105	152	45	10	257	27	358	342
Thrombophlebitis and pulmonary embolism								
Number	3	0	0	0	3	0	9	4
Percent	(2.7)	(0.0)	(0.0)	(0.0)	(1.1)	(0.0)	(2.4)	(1.1)
No thrombophlebitis and pulmonary embolism								
Number	107	161	45	10	268	28	368	361
Cardiac complications								
Number	0	3	0	0	0	1	2	10
Percent	(0.0)	(1.9)	(0.0)	(0.0)	(0.0)	(3.6)	(0.5)	(2.7)
No cardiac complications								
Number	110	158	45	10	271	27	375	355
Urinary tract complications								
Number	4	7	0	0	9	0	4	7
Percent	(3.6)	(4.3)	(0.0)	(0.0)	(3.3)	(0.0)	(1.1)	(1.9)
No urinary tract complications								
Number	106	154	45	10	262	28	373	358
Bleeding								
Number	2	9	1	0	10	0	17	10
Percent	(1.8)	(5.6)	(2.2)	(0.0)	(3.7)	(0.0)	(4.5)	(2.7)
No bleeding								
Number	108	152	44	10	261	28	360	355
Intraabdominal complication								
Number	11	24	4	0	14	4	33	39
Percent	(10.0)	(14.9)	(8.9)	(0.0)	(5.2)	(14.3)	(8.8)	(10.7)
No intrabdominal complication								
Number	99	137	41	10	257	24	344	326
General systemic complication								
Number	1	2	1	0	1	1	3	6
Percent	(0.9)	(1.2)	(2.2)	(0.0)	(0.4)	(3.6)	(0.8)	(1.6)
No general systemic complication								
Number	109	159	44	10	270	27	374	359

summarized in Table III. Due to differences in the number of patients responding "unknown" with respect to the number of cigarettes smoked and the length of time smoked, the total number of patients in a particular cell of Table III may differ slightly from the total number in the corresponding cell of Table II. Otherwise, Table III can be read in a manner similar to the interpretation given for reading Table II.

Focusing on any particular complication in Table III, the rate of complica-

TABLE III

Number of Cigarettes Smoked per Day, Age, Type of Complication

Type of complication	Nonsmoker		<10 cig.		11–20 cig.		21+ cig.	
	<50	50+	<50	50+	<50	50+	<50	50+
Atelectasis and pneumonia								
Number	5	9	9	3	14	11	11	11
Percent	(4.5)	(5.6)	(7.9)	(3.6)	(3.5)	(5.1)	(5.9)	(10.3)
No atelectasis and pneumonia								
Number	160	152	105	80	386	206	175	96
Thrombophlebitis and pulmonary embolism								
Number	3	0	1	0	7	3	4	1
Percent	(2.7)	(0.0)	(0.9)	(0.0)	(1.7)	(1.4)	(2.2)	(0.9)
No thrombophlebitis and pulmonary embolism								
Number	108	161	113	83	393	214	182	106
Cardiac complications								
Number	0	3	0	3	2	8	0	0
Percent	(0.0)	(1.9)	(0.0)	(3.6)	(0.5)	(3.7)	(0.0)	(0.0)
No cardiac complications								
Number	111	158	114	80	398	209	186	107
Urinary tract complications								
Number	4	7	3	2	7	4	3	1
Percent	(3.6)	(4.3)	(2.6)	(2.4)	(1.7)	(1.8)	(1.6)	(0.9)
No urinary tract complications								
Number	107	154	111	81	393	213	183	106
Bleeding								
Number	2	9	4	2	19	4	6	4
Percent	(1.8)	(5.6)	(3.5)	(2.4)	(4.7)	(1.8)	(3.2)	(3.7)
No bleeding								
Number	109	152	110	81	381	213	180	103
Intraabdominal complications								
Number	11	24	13	9	23	23	16	11
Percent	(9.9)	(14.9)	(11.4)	(10.8)	(5.7)	(10.6)	(8.6)	(10.3)
No intraabdominal complications								
Number	100	137	101	74	377	194	170	96
General systemic complications								
Number	1	2	3	2	1	4	1	1
Percent	(0.9)	(1.3)	(2.6)	(2.4)	(0.3)	(1.8)	(0.5)	(0.9)
No general systemic complications								
Number	110	159	111	81	399	213	185	106

tion fluctuates only slightly across age smoking habit categories except the rate for atelectasis and pneumonia appears to be higher in the 50 years or older, 21 or more cigarettes per day category. One unusual finding in a table of this size can be expected from random sampling alone, however, and in view of the lack of any systematic trend we conclude that the number of cigarettes smoked per day has no effect on the complication rate for these patients.

Finally, the data are classified by immediate postoperative survival time,

TABLE IV

Smoking Habits of Patients Classified by Age and Survival Time

Age	Smoking Habits	<30 days		>30 days		Total	
		No.	%	No.	%	No.	%
≤50	Smoker	0	0.0	110	100.0	110	100.0
	Nonsmoker	4	0.6	689	99.4	693	100.0
>50	Smoker	5	3.1	156	96.9	161	100.0
	Nonsmoker	8	2.0	395	98.0	403	100.0
Unknown		1	5.9	16	94.1	17	100.0
Total		18		1366		1384	

age, and smoking habits in Table IV. Again, there are no observable differences between smokers and nonsmokers.

Smokers were compared with nonsmokers with regard to length of stay in the hospital. There was no obvious pattern in differences between percentage of smokers and nonsmokers.

Summary and Conclusions

A cooperative study was conducted by the Veterans Administration with the express purpose of comparing four surgical procedures as a treatment regimen in patients with duodenal ulcer disease. Subsequently, a smoking history was recorded for 1441 of the 2988 patients in the series. This paper summarizes the analyses of the smoking phase of the study with regard to postoperative complications, including immediate postoperative mortality and length of postoperative hospital stay.

The results give no evidence of an association between smoking and complications, nor between smoking and operative mortality, nor between smoking and days to discharge. The most obvious trend is probably predictable, namely, patients over 50 have more complications and a higher mortality rate than those under 50.

In spite of the relatively large number of patients included in this report, the results must be viewed with considerable caution. The population studied is not representative of the general population. Indeed, the smoking habits, the age distribution, and disease rate in the population studied are quite likely to differ from the general population. More important, however, is the fact that these data were collected peripherally as a part of a study with a primary objective unrelated to this phase of the study. In fact, the collection of some of the smoking data began after the primary study had been underway for a number of years. Consequently, the method of data collection may have been altered in many instances, due to changing personnel, over the years. Some inconsistencies were found between smoking histories taken on the same patient at different times. This may have resulted from the quality and accuracy of the information given to the examiner by the patient.

In view of the foregoing discussion, few, if any, generalities should be drawn from this research. However, the results do merit consideration for future substantiation. Finally, it should be mentioned that these results apply only to immediate postoperative findings and do not apply to long-range effects of smoking upon the patient after surgery for duodenal ulcer disease.

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UNUSUAL PROBLEMS IN SURGERY

Multiple Small Bowel Perforations: An Unusual Complication of Trichobezoar

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Perforation of the small bowel by a bezoar of the intestinal tract is a rare occurrence. To our knowledge there has been only one such case reported in the literature (1). We recently operated upon a 22-month-old girl with a trichobezoar of the stomach and small intestine.

Case Report

A 22-month-old Black girl was admitted to The Mount Sinai Hospital in January 1970 for vomiting and constipation of six days' duration. The patient was well until six days prior to admission, when she became anorexic and vomited intermittently after meals. The vomiting increased in frequency and soon occurred after every meal; some weight loss was noted. There was no history of abdominal pain, hematemesis, melena, fever, or urinary tract symptoms. Her grandmother had noticed that the child was eating hair from hair brushes and foam rubber hair rollers, as well as her own hair, which she pulled from her scalp.

The patient was the second child born to a 21-year-old unmarried mother and was cared for by her grandmother. Her growth and development were apparently within normal limits. Examination of the child on admission revealed a well-developed, thin, slightly dehydrated Black girl with relatively

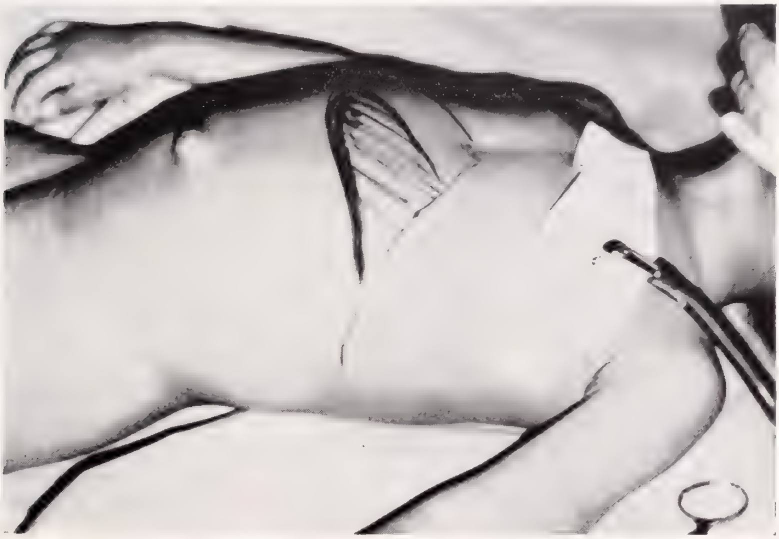

FIG. 1. The epigastric mass is outlined on the child's abdomen.

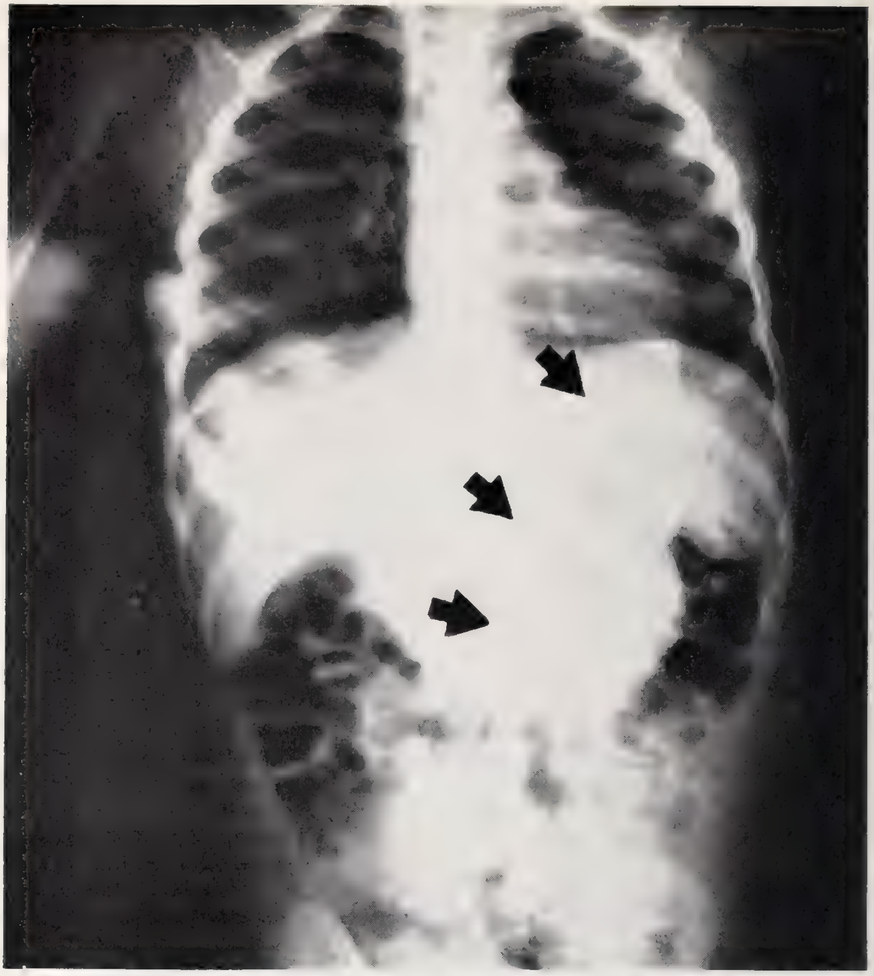

FIG. 2. Plain film of the abdomen. Note the mottled appearance of the stomach (arrows).

short hair, in no acute distress. Her pulse rate was 120 beats per minute, respirations were 24 per minute, and her temperature was 99.2°F. Significant physical findings were limited to the abdomen, where a large, firm, oval, non-tender, movable mass was palpable in the epigastrium and the left upper quadrant (Fig. 1). There was no abdominal distention, guarding, rigidity, or tenderness. The bowel sounds were hypoactive. The rectal examination was unremarkable.

Laboratory studies were as follows: The hemoglobin concentration was 8.2 gm. per 100 cc and the white blood cell count was 16,000/mm^3. The differential count was 67 polymorphonuclear leucocytes, 1 band, 23 lymphocytes and 9 monocytes. Urinalysis and serum electrolytes were within normal limits. Plain films of the abdomen showed mottled, bubbly particulate matter in the stomach (Figure 2). There was no evidence of intestinal obstruction. An upper

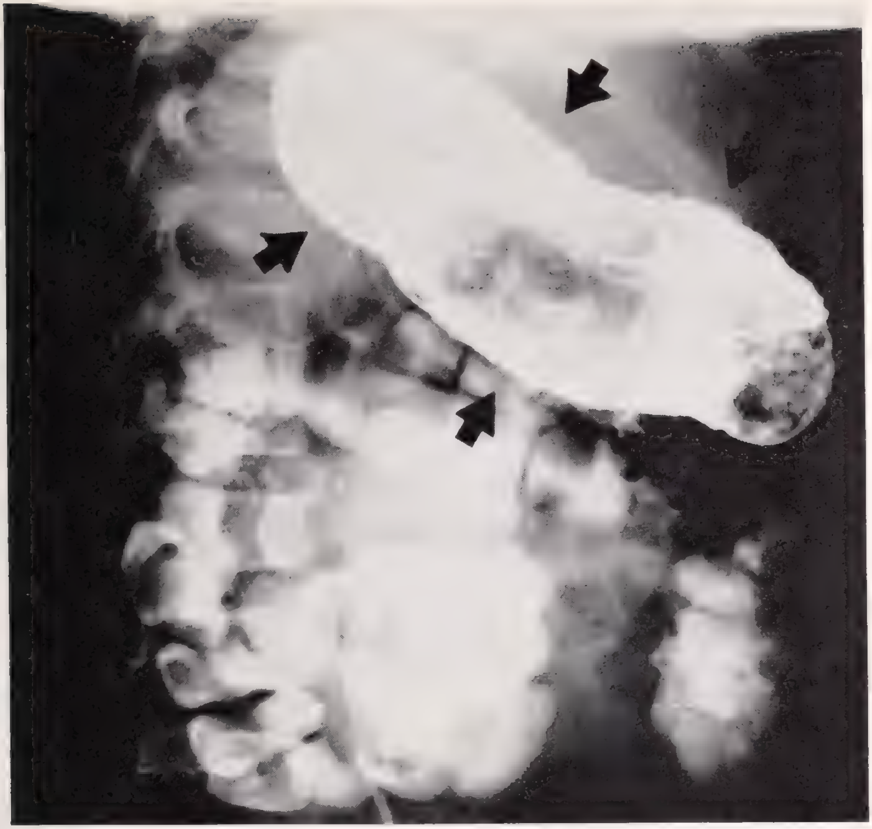

FIG. 3. Gastrointestinal series. A radiolucent foreign body is seen within the stomach (arrows).

gastrointesinal x-ray study was performed and revealed a radiolucent foreign body which filled the stomach (Fig. 3).

The child was prepared for surgery. At exploration, a large bezoar was found which conformed to the shape of the stomach. A long cord-shaped tail extended into the small bowel. The small bowel was tightly reefed up over this tail-like extension along its mesenteric border. During the course of exploration, numerous small intestinal perforations which were sealed off by adjacent loops of small bowel and mesentery, opened spontaneously and contaminated the peritoneal cavity. There were eleven perforations measuring from 0.5 to 2.5 cm in diameter; all were located along the mesenteric border. Through the perforations one could see the tail of the bezoar which was composed of hair, threads, strings, and plastic material (Fig. 4). A gastrotomy was performed and the main body of the bezoar was removed. The tail was removed through two separate jejunotomy incisions. Because of multiple perforations and several impending perforations, 3½ feet of the proximal small bowel were resected and an end-to-end anastomosis was performed 14 inches from the ligament of

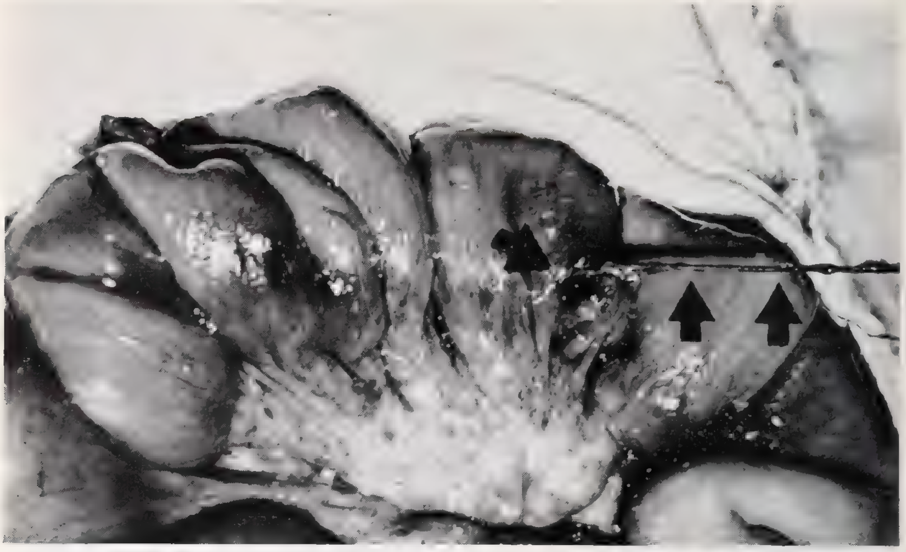

FIG. 4. Operative photograph. The tail of the bezoar (arrows) has been withdrawn from a perforation in the jejunum (arrow).

Treitz. The peritoneal cavity was irrigated with copious amounts of warm saline. There were 5 feet of small bowel remaining at the completion of the operation.

The resected specimen (Fig. 5) consisted of a 40 inch segment of jejunum with multiple perforations along the mesenteric border. The serosa adjacent to the perforations was hemorrhagic and partially covered with a thick yellow exudate. The mucosa was diffusely congested. There were hemorrhages and linear ulcerations along most of the specimen. The bezoar (Fig. 6) measured 11 × 14 cm and was composed of hair, string, thread, and synthetic fibers—all embedded in a white rubbery sticky material which had the shape of the stomach with a tail-like extension.

The child's postoperative course was complicated by a right lower lobe pneumonia which responded to antibiotic therapy. She recovered completely in three weeks and began to gain weight.

Discussion

A bezoar is a concretion formed in the stomach or intestine in ruminates and occasionally in man. Bezoars are composed of any indigestible material or from large amounts of poorly digestible material. More than half of all bezoars are trichobezoars which are composed of ingested hair. Forty percent are phytobezoars which consist of masses of indigestible vegetable matter. Trichophytobezoars are a combination of hair and vegetable matter. Concretions, which are composed of tar, shellac and resins, comprise only a small percentage of bezoars. Trichobezoars are rarely found in man. Since Baudamant first described this condition in 1779 (2) more than 200 cases have been reported in

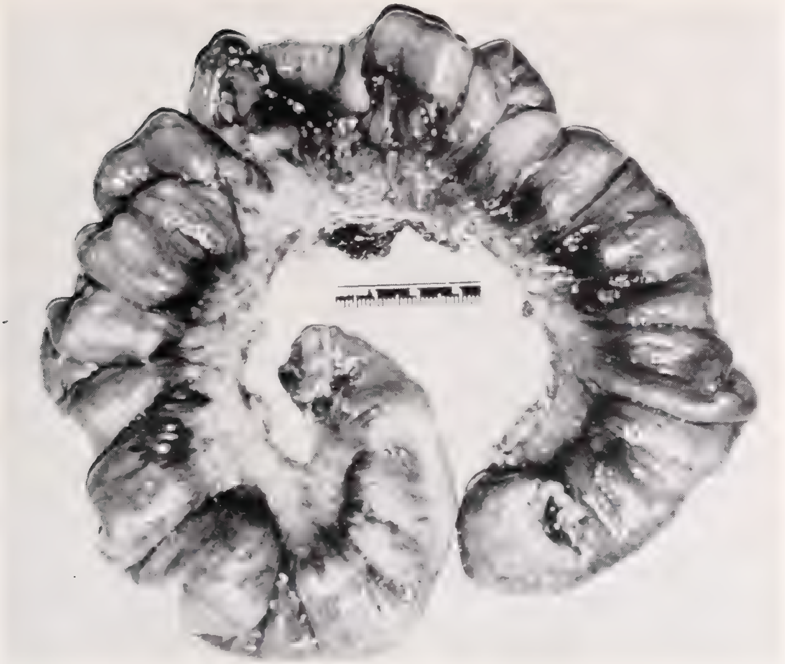

FIG. 5. Resected specimen. Forty inches of jejunum were removed. Note linear hemorrhages along the mesenteric border.

the medical literature (3–11). In 1938, DeBakey and Ochsner (6) presented a comprehensive view of the world literature in which they collected 171 cases of trichobezoars and added one case of their own. Schonborn (12) reported the first case of trichobezoar removed at surgery in 1883. Stelzer (6) made the first correct preoperative diagnosis in 1896.

Trichobezoars are found in emotionally disturbed or mentally retarded persons in whom trichophagia is a common occurrence. However, in less than 10% of cases, a definite deviation from psychologic norms has been noted (3); 18% of cases occurred during the first decade of life, 37% during the second and 27% in the third (6). More than 80% of the cases occurred before the age of 30 years. The earliest occurrence was reported by Gaston (6) in a 1-year-old infant and the oldest in a 59-year-old woman (6). The great majority of patients are girls or young women.

The characteristic clinical manifestation of trichobezoar is a large, firm, freely movable epigastric mass. This may be associated with pain, nausea and vomiting, anorexia, weakness, loss of weight, constipation or diarrhea. In a series of 131 cases (6) an abdominal mass was present in 88%; abdominal pain in 70%; nausea and vomiting in 65%; weakness and loss of weight in 38% and constipation and diarrhea in 32%. Frequently few or no symptoms referable to the stomach are observed. The diagnosis is not difficult to establish if the condition is borne in mind. Careful questioning will most often uncover

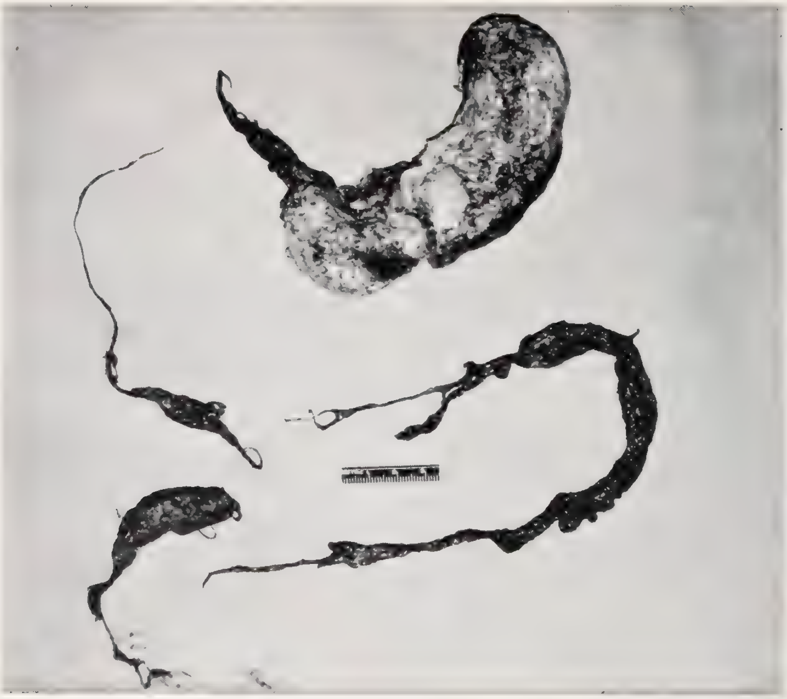

FIG. 6. Bezoar and tail removed from the stomach and jejunum.

clues which suggest a history of trichophagia. Although the patient usually denies eating hair, this information can be obtained from parents or relatives (6). The presence of an epigastric mass is corroborative evidence. An upper gastrointestinal series employing a small amount of thin barium will show characteristic findings. Occasionally, a plain film of the abdomen is all that is necessary to establish the diagnosis.

The treatment of choice is prompt surgical removal of the bezoar. The mortality rate following surgery in cases with complications is 53.1%; in those cases without complications the corresponding figure is 10.4%. The overall mortality in all collected cases of trichobezoar is 19.1% (6). Complications are due primarily to intestinal obstruction and traumatic irritation to the stomach and bowel wall which may be followed by mucosal erosion, gastrointestinal bleeding, ulceration, perforation, and peritonitis (13). In the collected cases of trichobezoar, intestinal obstruction occurred in 10.8%, gastroduodenal ulceration in 9.6%, perforation of an ulcer in 3.2%, and peritonitis in 3.8% (6).

Not infrequently two or more intragastric masses are found (5, 7). In 4.9% of cases more than one hair tumor was found in the stomach and in 14.6% of cases there were hairballs found in the intestinal tract (7). Therefore, a thorough exploration of the stomach and intestines is imperative in order to be absolutely certain that all foreign bodies have been removed.

Surgical removal of a bezoar is symptomatic therapy. The condition is psychological in origin and therapy is only begun with the removal of the hairball (14). In view of a significant rise in the mortality following occurrence of complications in trichobezoar, the importance of early diagnosis and surgical removal of the hairball cannot be overemphasized.

Summary

The case history of a child with a trichobezoar of the stomach and multiple perforations of the small bowel caused by a taut, tail-like extension of the bezoar into the small bowel is presented. This is the second case reported in the world literature.

The importance of early diagnosis and surgical removal of the bezoar to reduce morbidity and mortality due to complications is emphasized.

SUK K. KIM, M.D. and A. ROBERT BECK, M.D.

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CLINICO-PATHOLOGIC CONFERENCE

Fever, Lymphadenopathy, and Bone Involvement in a Child

Edited by
FRANKLIN M. KLION, M.D.

A four-year-old Negro girl was admitted to The Mount Sinai Hospital for loss of weight and fever of five days' duration.

The patient's growth and development was normal, and the patient was well until approximately four weeks prior to admission, when the mother noted that the child became anorexic and was "getting thinner." An eight-pound weight loss was noted over a six-month period. One week prior to admission the child complained of pain in her abdomen and right leg. At this time the mother noted a lump on the child's forehead and right elbow. Five days prior to admission the mother noted a fever of 102°F which persisted until admission.

The patient had measles and chicken pox two years earlier. There were no other significant illnesses. The child lived in South Carolina from age six months to one year. She had no known contact with contagious diseases or household animals.

The patient appeared acutely ill with respiratory distress. The pulse was 110/min and regular, blood pressure 80/60, respirations 38 and labored, temperature 102°F. There were areas of increased pigmentation on the chest. The conjunctivae were pale and fundi were not visualized. The spine was not tender, and the thyroid was not palpable. The lungs were normal. Dullness was noted for 2 to 3 cm to the right of the sternum. A Grade 1/6 short systolic murmur was noted at the pulmonary area. A nontender liver was palpated 3 cm below the right costal margin. The spleen was not palpated. The genitalia were normal. A 5 cm soft, slightly tender, and movable mass was palpated in the right epitrochlear area, and severe large, nontender lymph nodes were palpated in the cervical, axillary, and inguinal areas. No bone masses or tenderness were noted. Neurologic examination was normal. The hemoglobin was 7.0 G%, white blood cell count 26,600/mm^3, with 83% segmented neutrophils, 7% band forms, 4% lymphocytes, 1% monocytes, 1% metamyelocytes, and 4% myelocytes. The urine specific gravity was 1.015, acid. No albumin, sugar or acetone were found. The microscopic examination revealed 2–3 red blood cells and 8–9 white blood cells per high power field, and many epithelial cells. A lumbar puncture showed clear fluid which later became bloody and contained 950 cells. The spinal fluid protein and glucose were normal. Cultures showed no growth and no organisms were seen. The total serum protein was 6.7 G%, albumin, 2.5 G%, and globulin 4.2 G%. The sedimentation rate was 76 mm/hr. The uric acid was 3.9 mg%, SGOT 66 units, bilirubin 0.5 mg%, calcium 8.4 mg%, phosphorus 4.1 mg%. The prothrombin time was 14 sec (12.5 control), creatinine 1.4 mg%, alkaline phosphatase activity 24.4. Electrophoresis of the serum showed a low albumin and deviations of the α_1, α_2, and gamma globulin. The hemoglobin ranged from 5 to 7 G%. The white blood cell count ranged from 12 to 20,000/mm^3 with a shift to the left. The platelet count was 216,000/mm^3, and a Coombs' test was negative. The reticulocyte count was 1.8%. A sickle-cell preparation was positive. Hemoglobin electrophoresis showed A and S hemoglobin. A bone marrow showed normocellular erythroid hyperplasia; no tumor cells were noted. Cultures were negative for pathogens and for acid fast bacilli.

The patient had a febrile course with almost daily spikes to 101–103°F. Numerous blood cultures were negative. Stool, nose, and throat cultures were unrevealing. Skin tests for tuberculosis, intermediate and second strength, blastomycosis, histoplasmosis, coccidiomycosis were all negative. A Frei test was negative. Febrile agglutinins were negative. A heterophil test was negative. A Kveim test was negative. The patient had a biopsy of the left epitrochlear and the right eiptrochlear node which showed nodular histiocytic hyperplasia and microabscess formation. No microorganisms were seen on special stains.

Cultures taken from the nodes were sterile. A complement fixation test for Brucella and Pasteurella were negative. Since the pathology was thought to be compatible with Pasteurella, the patient received a ten day course of tetracycline therapy without noticeable improvement. The patient continued to spike temperatures intermittently.

One month later a biopsy was taken from a lytic lesion in the frontal bone noted on x-ray.

*Dr. Arnold Rubin**: This young Negro child presented with a subacute illness characterized by loss of weight and fever over a six-month period. On examination she had hepatosplenomegaly, lymphadenopathy, a leukocytosis, and anemia. There was a slight elevation of gamma globulin.

She continued to show a severe anemia, probably unrelated to the sickle trait. A rather extensive work-up for infection was not fruitful. All skin tests and agglutinin studies were negative. Because of the possibility of an infectious process, namely pasteurellosis, the patient was given a course of tetracycline therapy without any effect, and she continued to run a fever. Then an x-ray of the skull revealed a lytic lesion, and a bone biopsy was taken which I assume led to the diagnosis.

The diagnostic possibility here lies between an infectious or a neoplastic process. Ordinarily one does not expect lytic bone lesions in an infection, but of course, osteomyelitis can be destructive. How can one identify neoplasia? This must be considered a process in which normal tissue is invaded and usually destroyed by foreign cells. Suppuration may cause tissue destruction but an organism should be recognized. In the present case, bacteriologic studies were negative and there was no response to antibiotics. Therefore, there was no evidence of a bacterial or fungal infection. However, our current concepts of viral infections have made the distinction between neoplasia and this type of infection less clear. This patient appeared to have a neoplastic process characterized by invasion and destruction of tissue by foreign cells rather than suppuration or replacement with inflammatory tissue.

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The lymph node biopsy showed hyperplasia with many reticuloendothelial cells of histiocytes. The microabscesses were most likely areas of inflammatory tissue which were not suppurative. You are all well aware that lymph nodes have a distinct architecture with a cortex containing germinal centers with reticulum cells and plasma cells surrounded by areas which consist of small lymphocytes. There is a separation between cortex and medulla which also contains reticulum cells. A marginal sinus along the periphery of the node is free of cells. There is also a connective tissue envelope which contains only connective tissue cells. In other words, the lymph node cells should be retained within the node, not in the marginal sinus, and the architecture in terms of separation of the cortex and medulla should be maintained. When this architecture becomes effaced, usually due to the proliferation of one cell type, or perhaps a mixture of a few cell types, and shows invasion of the capsule, a diagnosis of lymphosarcoma is considered. If the process which is replacing the lymph node is a reticulum cell, it is called "reticulum cell sarcoma." The biopsy of the node was not reported as showing a lymphoma or reticulum cell sarcoma. I must therefore consider this child had a reticulosis or reticuloendotheliosis, often difficult to distinguish from reticulum cell sarcoma.

In the immune response, reticulum cells play a major role. They are very active in phagocytosis and they appear to be important in processing antigens and delivering some sort of immunogenic message to lymphocytes. Monocytes can transform into macrophages in vitro, and actually some of these cells look just like histiocytes, so that the distinction which can usually be made morphologically may have little functional significance. I therefore consider reticulum cells, histiocytes, monocytes, and macrophages as expressions of one cell type, the appearance of which depends upon its location and functional activity at one particular time.

On the other end of the immune response, the so-called efferent side, the lymphocyte, having been activated and proliferating in response to immunogenic material, produces a series of humoral substances, one of which has been called "MIF" (or macrophage inhibiting factor). This humoral material seems to recruit the macrophages (monocytes) as they pass, and induces them to create an inflammatory reaction. The MIF factor is not specific, but the activation of the lymphocytes to produce this factor is specific. Therefore, the macrophages are very important in at least two sites in the normal immune response where they interact with lymphocytes.

Certain characteristics describe the reticuloendothelial cell functionally. They have the ability to phagocytize, to adhere to glass, to show pseudopodic projections, and they have receptor sites for gamma globulin (Tables I, II).

The reticuloendothelioses are categorized in Table III. Subacute bacterial endocarditis would be a good example of a secondary reticuloendotheliosis.

There is usually a diffuse type reticuloendothelial hyperplasia which may be marked. In Gaucher's disease, histiocytic cells are full of lipid material, and presumably they proliferate in an attempt to dispose of lipid which cannot be metabolized because of an enzyme defect. Although this type of proliferation

TABLE I

Reticuloendothelial Cells

Reticuloendothelial cells
  Macrophages ↔ Monocytes
  Histiocytes
  Reticulum cells
Function: Phagocytosis
  1. Clearing and metabolizing "debris"
  2. Host defense
    a. Ingestion and Processing of Antigens "superantigens" in Immune Response
    b. Cellular Immunity—reaction to MIF produced by lymphocytes
Characteristics
  1. Phagocytosis
  2. Adherence to glass
  3. Pseudopodic projections
  4. Gamma globulin receptor sites

TABLE II

Features which Distinguish Lymphocytes from Reticulum Cells

	Lymphocytes	Reticulum cells
Morphology	Deceptive & Irrelevant	
Movement	By foot process	Ameboid or undulating membrane process
Ultrastructure	Few ribosomes simple	Well developed Golgi plus lysosomes
Phagocytosis particles	No	Yes
Adherence to fibers	No	Yes
Immunoglobulin synthesis	+++	±
Response to mitogenic stimulation	Yes	No

TABLE III

The Reticuloendothelioses

1. Reactive—2° to infection or "storage" disorder
   Examples: SBE
   Gaucher's disease
2. Reticulum cell leukemia or "malignant" reticuloendotheliosis.
   Functionally monocytic leukemia
   Distinguished from reticulum cell sarcomatosis only by its tendency not to form cohesive masses. Skin lesions show infiltration in deep dermis around appendages.
3. Histiocytosis
   Localized—eosinophilic granuloma
   Generalized—Schüller-Christian's disease—chronic Letterer-Siwe's disease—acute

may be considered hyperplastic or secondary, it may present clinically as malignant disease such as reticulum cell sarcoma.

The reticuloendothelioses or reticuloproliferative disorders include several types of malignant transformations of the reticulum cell. Reticulum cell sarcoma is one. For simplicity, one might define reticulum cell sarcoma as a disease which tends to form mass lesions rather than to diffusely infiltrate tissues. The cells usually show bizarre forms. Another of the reticuloendothelial tumors is Hodgkin's disease, where mass lesions are found and a mixture of reticulum cells and lymphocytes are characteristic.

Some of the diffuse types of reticuloendothelioses may be indistinguishable from reticulum cell sarcoma in that the cells are bizarre and the clinical course may be quite malignant. Other types have a more benign course where the reticulum cell infiltration shows smaller, and apparently more differentiated, cells.

We have renamed some forms of leukemic reticuloendothelioses as "reticulolymphocytic leukemia." This appears to be a hybrid disease with diffuse infiltration of the blood, marrow, spleen, liver, and sometimes lymph nodes, by a type of cell that bears characteristics both of reticulum cells and lymphocytes. With the scanning electron microscope, it looks more like a reticulum cell than a lymphocyte. The cell does not show the foot process movement, but rather has fine pseudopodic extrusions, like a reticulum cell. On the other hand, it responds to phytohemagglutinin and it synthesizes immunoglobulins, characteristic of lymphocytes. These diseases seem to be primary as no predisposing problem can be identified.

I do not think this patient had lymphosarcoma, because of the lymph node morphology and because the cells did not appear bizarre. There was no leukemic process either. Therefore, the patient had a diffuse, non-leukemic type of reticuloendotheliosis. I would like to consider the diffuse type of reticuloendotheliosis, which has been called histiocytosis. When localized, it is eosinophilic granuloma; when generalized, it is Schüller-Christian disease; when disseminated, it is Letterer-Siwe disease (Table IV). It can develop at any age. Usually the most malignant form of the disease is found in young children. The older the patient is, the more the tendency to be localized, so that Letterer-Siwe disease is a disease of very young children, whereas eosinophilic granuloma and Schüller-Christian disease are found at a later age.

The chronicity and aggressive nature of the disease is not related to the cell morphology. Characteristically, all bones, lymph nodes, liver, and spleen may be involved. In the eosinophilic granuloma, however, one commonly finds only bony involvement. In the more chronic forms, there may be pituitary or hypothalamic involvement and diabetes insipidus. The pituitary gland, however, is usually not directly involved by cellular infiltration, and it is not common to find destruction of the bony processes. Only rarely does panhypopituitarism result.

Mucocutaneous involvement may be manifested by an eczematous type of eruption, but may be seborrheic or hemorrhagic. Mucous involvement results in loose teeth, and peridontal disease in a young child reflects generalized dis-

TABLE IV

The Histiocytoses

	Eosinophilic Granuloma	Schüller Christian's	Letterer-Siwe
Age	Young adult	Young adult	Child
Skin	–	Lesions	Lesions characteristically subepidermal
Bone lesions	+	+	+
Marrow	–	–	+
Organs enlarged	–	+ or –	+
Oral lesions	+	+	+
Chronicity	++++	++	±
Microscopic	Eosinophiles & histiocytes	Lipid laden histiocytes with eosinophiles	Histiocytes
Architecture of lymphoid tissue	Diffuse involvement—may leave architecture intact		
Treatment	None or radiation	Chemicals or radiation	Chemicals
Prognosis	Long survivors	Many long survivors	Few long survivors
		← TRANSITIONS →	

ease due to destruction of the alveolar bone by invasion with histiocytic cells. There also may be ulcerations of the mucous membranes which fail to respond to antibiotics, but do respond to prednisone. In the more acute and aggressive form of the disease, the marrow may be diffusely involved in a leukemic-like process. The lungs may also be involved. Many of these patients respond dramatically to treatment, and unlike leukemia, may often be cured. The disease is sensitive in most cases to prednisone, vinca alkaloids, and to methotrexate. Treatment more often controls the disease, and in about a third, the mild cases may be cured. In another third, I think the disease tends to be chronic and rather indolent. In the last third, it is aggressive and progressive, and treatment may not be effective.

I think that the patient had histiocytosis, probably of the more diffuse variety.

Dr. Cyril Toker[*]*:* Thank you Dr. Rubin. Are there any questions?

Question: What is the basic difference between the histiocytes seen in the various diseases classified in the reticuloendotheliosis?

Dr. Rubin: The distinction is not clear-cut. In reticulum cell sarcoma, the cell is less differentiated. The nucleus tends to be more euchromatic, larger, and more bizarre-looking. In histiocytosis the cells are foamy with small nuclei, and seem more differentiated.

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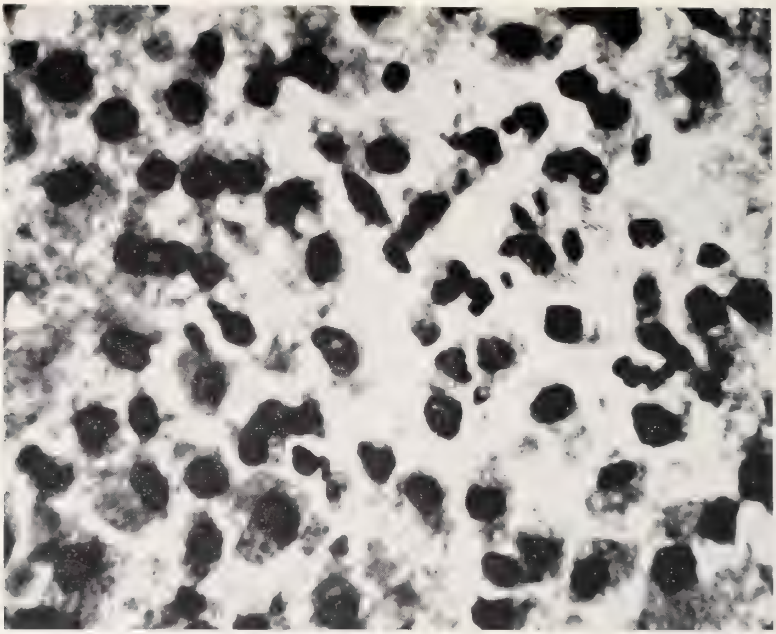


FIG. 1. Sheets of uniform cells with pyknotic nuclei (H and E ×320).

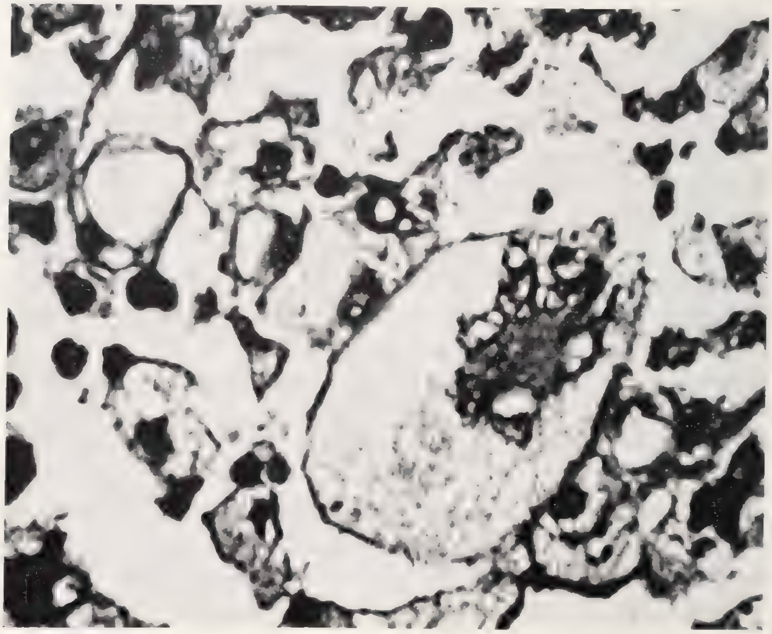


FIG. 2. Large lipid containing histiocyte (H and E ×320).

Question: Do you think they are the same cells?

Dr. Rubin: Yes.

Dr. Toker: Again to examine a normal lymph node, the germinal centers are inhabited by reticulum cells which have large, pale-staining nuclei. The medulla is composed predominantly of lymphatic cords in between which the lymph flows in the sinusoids. A major inhabitant of the lymphatic cords of the medulla is the histiocyte. Notwithstanding Dr. Rubin's comments, we still distinguish between a histiocyte and a reticulum cell. The histiocyte has abundant cytoplasm and a small, darkly stained nucleus; it is a far less active cell than the reticulum cell, although, as has been indicated, these cells may possibly be interchangeable.

The lymph node biopsy from this patient showed a complete loss of architecture. Nodular aggregates of cells of rather uniform appearance (Fig. 1), extended out beyond the capsular area into perinodal fat. Within the lymph node were aggregates of segmented leukocytes in necrotic areas of tumor. These were called microabscesses and suggested the possibility of an infective process. This degree of segmented leukocytic aggregation is not common in the histiocytoses, but may occur. The cells within the node were uniform and closely resembled normal histiocytes, with small nuclei and abundant eosinophilic cytoplasm. Lipid-containing cells were present (Fig. 2).

Some of the cells showed vacuolization by lipid accumulation.

The biopsy from the frontal bone showed an infiltrate in which histiocytes were prominent, but were intermixed with other leukocytes and plasma cells. These very large and plump histiocytic cells contained lipid material classical of the cells seen in Hand-Schüller-Christian disease. We have abandoned the distinctions made between eosinophilic granuloma, Hand-Schüller-Christian, and Letterer-Siwe disease, and between the lipid and nonlipid histiocytosis, since they have not proved of value, and consider these lesions in terms of whether they are localized or generalized.

In summary, then, this patient had a generalized histiocytosis. The subsequent course is of interest. Following antibiotic therapy which was of no benefit, the patient was put on steroid therapy, with a dramatic response. Three years ago steroids were discontinued, and the patient is now well after a period of eight years since the commencement of her illness.

Final Diagnosis:

HISTIOCYTOSIS X.

RADIOLOGIC NOTES

CLAUDE BLOCH, M.D. AND HARVEY M. PECK, M.D., COEDITORS

Case No. 354

A 20-year-old unmarried woman experienced the sudden onset of diffuse abdominal pain and pain in the left shoulder. She was referred to the hospital for admission, and to the X-Ray Department for a simple film of the abdomen prior to being sent to her hospital bed. Her last normal menstrual period was six weeks prior to admission. Some atypical vaginal bleeding started the day prior to admission.

The patient fainted in the X-Ray Department after a single supine film of the abdomen was obtained. Examination revealed a blood pressure of 80/60, pulse 100. She was immediately transported to the hospital floor and into the care of her referring physician.

Simple supine film of the abdomen (Fig. 1) showed signs of fluid in the abdomen including obliteration of the hepatic and splenic angles, lateral bulging of the lower peritoneal stripes, increased soft tissue density lateral to the margins of the ascending and descending colon, and increased soft tissue density above the bladder in the pelvis convex laterally on each side. In addition, a tampon was noted in the vagina. The diagnosis of ruptured ectopic pregnancy was considered most likely.

The hematocrit was 28% and the hemoglobin 9.8 grams. The patient was explored and a ruptured right tubal pregnancy was discovered. Approximately 1000 cc of blood was present in the peritoneal cavity. No other abnormality was noted. The postoperative course was unremarkable.

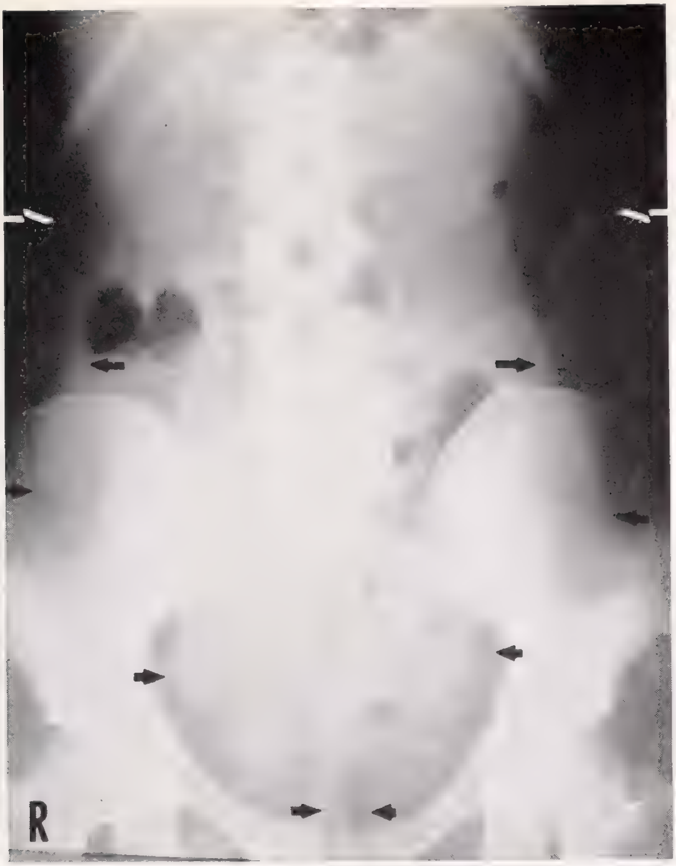
Discussion

When a young woman gives a history of six to eight weeks of amenorrhea followed by abdominal pain and some unusual vaginal bleeding, a tubal pregnancy is of course a prime consideration. This case is of particular interest in that the radiologist was the first one to suggest the correct diagnosis on the basis of the simple film of the abdomen. The film demonstrated all of the classical signs of fluid in the abdomen. The recognition of the shadow of a tampon in the vagina establishes vaginal bleeding in a young female. When such an individual is referred to the X-Ray Department for abdominal pain and then proceeds to faint, the conclusion is obvious. Another possibility might be a functioning ovarian tumor or cyst which has ruptured or twisted.

Case Report: RUPTURED ECTOPIC PREGNANCY—PLAIN FILM DIAGNOSIS

Acknowledgment

This case is presented through the courtesy of Dr. Marvin Thalenberg, Good Samaritan Hospital, Suffern, N. Y.

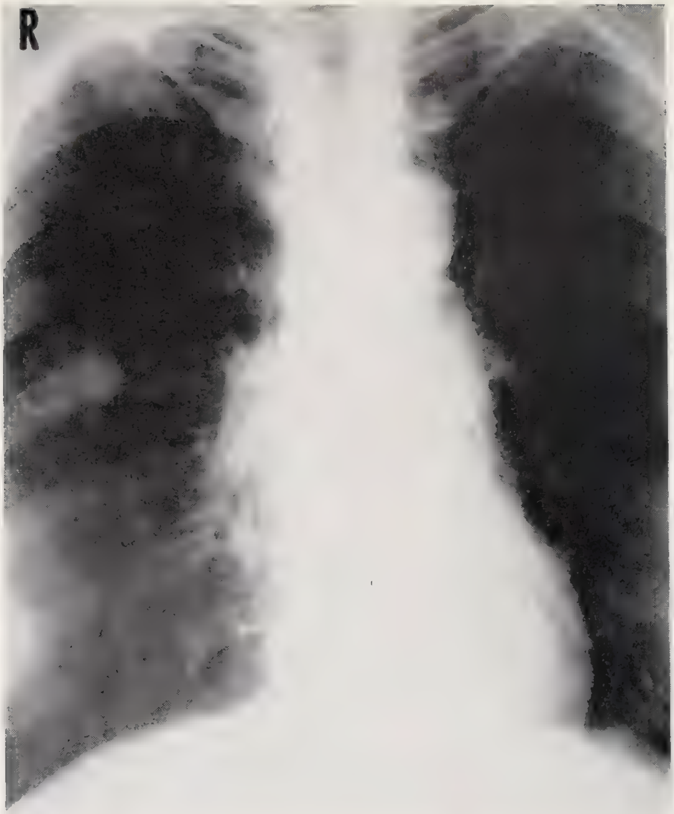


Case 354, Fig. 1. Simple supine film of the abdomen shows all the classic signs of fluid in the abdomen. The splenic and hepatic angles are obliterated (white arrow). There is increased soft tissue density lateral to the margins of the ascending and descending colon separating the bowel from the extraperitoneal fat lines (arrows). The lower lateral peritoneal stripes are bulging slightly (arrows). There is soft tissue density in the pelvis above the bladder convexed laterally on each side (arrows). This is more marked on the right where the actual tubal mass was located. There is a vertically oriented lucent structure overlying the lower pelvis in the midline just above the pubic symphysis (arrows). This is a distinctive radiographic appearance and represents a tampon in the vagina. Also noted is a slight generalized increased radio-density overlying the lower abdomen and pelvis.

Case No. 355

A 62-year-old woman was admitted to the hospital for evaluation of a lesion in the lung found on a routine chest X-ray. History and physical examination revealed no pertinent or significant findings. The patient was asymptomatic. She had never had a previous chest X-ray.

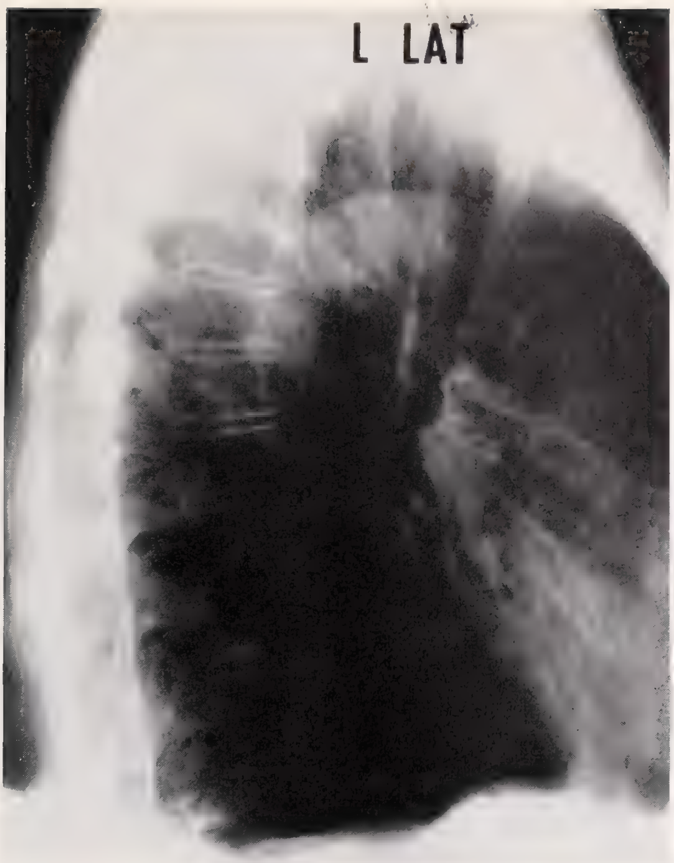
In the hospital, an extensive laboratory and radiographic evaluation revealed



Case 355, Fig. 1. Posteroanterior view of the chest shows a 3.5 cm rounded mass in the right midlateral lung field. The margins seem smooth on the medial aspect but seem to fade off on the lateral aspect. There appear to be some ill-defined lucencies overlying the mass. No calcifications are seen.

no pertinent findings except for the radiographic studies of the chest. Conventional films (Figs. 1 and 2) and laminograms (Fig. 3) were performed. A 3.5 cm mass lesion was delineated in the superior segment of the right lower lobe. The margins were smooth, somewhat lobulated, and sharply delineated from the surrounding lung. The lesion did not abut the pleura. There were no calcifications. A peculiar pattern of streaky lucencies was noted within the substance of the lesion, best demonstrated on the laminograms, suggesting breakdown of tissue. Beginning cavitation in a neoplastic or inflammatory mass was therefore suggested.

Thoracotomy and right lower lobectomy were performed. A photograph of the bisected mass (Fig. 4) confirmed the sharp separation of the mass from the surrounding lung and the smooth undulating margins. There were numerous spaces within the substance of the mass creating a cerebriform pattern. These spaces were empty of solid or liquid matter, thus apparently gas-containing.

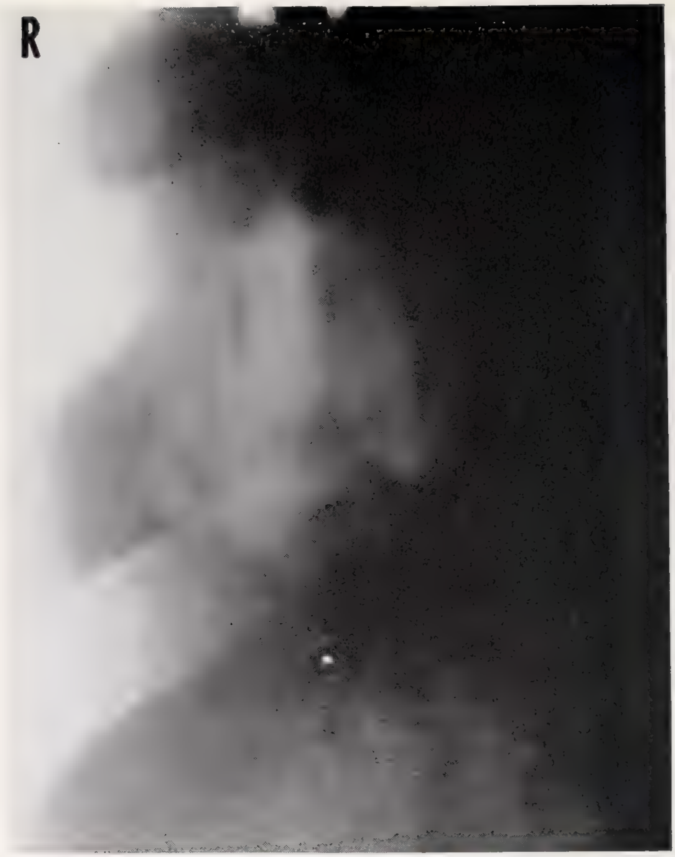


Case 355, Fig. 2. Left lateral view of the chest shows the posterior location of the mass corresponding to the apical segment of the right lower lobe. The margins are smooth and slightly lobulated in this projection. The mass is separated from the posterior chest wall and pleura. (The right rib cage is projected more posteriorly than the left on this well-positioned left lateral view.)

The bronchial tree was carefully dissected, but a bronchial connection to the mass could not be demonstrated. Histologically, the tumor mass was composed on chondromyxoid tissue covered by a single layer of alveolar cells. There was no evidence of ossification or calcification and no lymphoid tissue or fat was observed. The pathologist thus favored classifying the lesion as a bronchial chrondroma rather than a form of pulmonary hamartoma.

Discussion

Nosology of cartilage-containing tumors of the lung has been controversial (1, 2). A variety of names have been employed including hamartoma, chondroma, adenochondroma, chondromatous hamartoma, and mixed tumor. It would appear that a spectrum of histologic patterns accounts for the spectrum

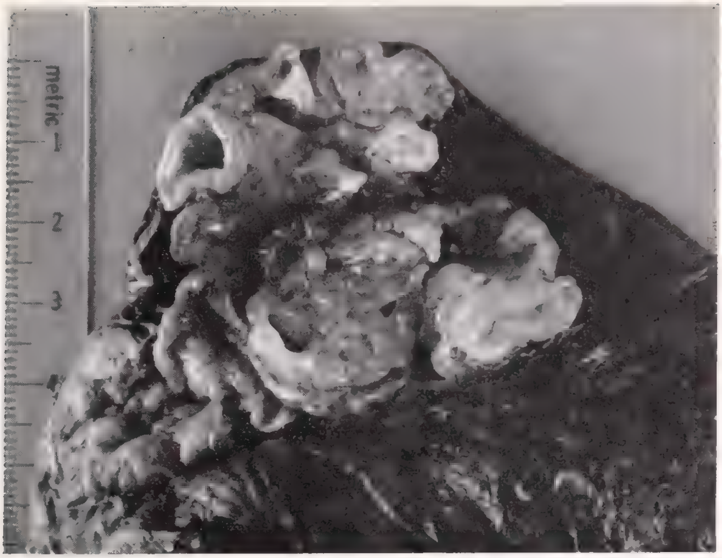


Case 355, Fig. 3. Laminogram in the frontal projection (4½ cm above table-top, patient supine) is thru the center of the mass. All margins are smooth, slightly lobulated, and sharply separated from the surrounding lung tissue without evidence of infiltration. There are linear and curvilinear lucencies throughout the mass suggesting clefts and interstices within its substance. No calcifications are demonstrated.

of terms employed. Virtually all tumors contain cartilage. Some tumors contain only cartilage with little or no other connective tissue elements or epithelial tissue, while others contain considerable amounts of a mixture of connective and epithelial tissues. Furthermore, the tumor may have an intrapulmonary or endobronchial location. A simple and practical approach considers all of these lesions as variations of the same tumor—hamartoma (3–5).

The lesion is usually in a peripheral location in the lung and as such is almost always asymptomatic. When in an endobronchial location, of course, mechanical symptoms result (6, 7). The tumor is felt to originate from an embryonic rest and has no significant malignant potential.

The roentgen features include a slightly lobulated margination, which is a reflection of the lobular pattern of cartilagenous growth. There is no capsule but



Case 355, Fig. 4. Photograph of the bisected mass shows smooth undulating margins and sharp separation from the surrounding lung tissue. A network of spaces creates a cerebriform configuration. These spaces did not contain any solid or liquid material or fat and presumably were filled with gas. A bronchial connection could not be demonstrated.

there is a sharp transition zone of connective tissue between normal lung and the tumor itself. This most often produces a very sharp margin on the roentgenogram which, when present, is a reasonably reliable sign of benignity. However, this transition zone need not be quite so abrupt; and, not infrequently, the margins are less sharp and thus equivocal from the roentgen viewpoint. About one-fourth of these lesions calcify to some extent.

Calcifications resembling popcorn occasionally occur which are highly characteristic (8). Cavitation is extremely rare (9).

Another characteristic growth pattern of this lesion produces "lobules of connective tissue and cartilage (are) partially or completely separated by clefts and spaces lined by various types of respiratory epithelium . . . and similar clefts are a constant feature around the edge of the tumor" (8). Although this growth pattern is quite common, the resulting roentgen pattern is apparently quite rare. The case presented demonstrates the unusual roentgen pattern of a tumor with clefts and interstices within its substance. These radiolucencies were best demonstrated with laminography and were apparently gas-filled, rather than fat-containing, as has been suggested (10, 11).

Other conditions in which a peculiar pattern of radiolucencies appears within a discrete lesion include necrotic malignant neoplasm, pulmonary cavity with mycetoma or fungus ball, necrosis in a chronic or acute inflammatory mass, and pulmonary cavity containing blood clots.

Case Report: PULMONARY CHONDROMATOUS HAMARTOMA WITH RADIOLUCENT CLEFTS.

Acknowledgment

This case is presented through the courtesy of Dr. A. S. Moscarella, Good Samaritan Hospital, Suffern, N.Y.

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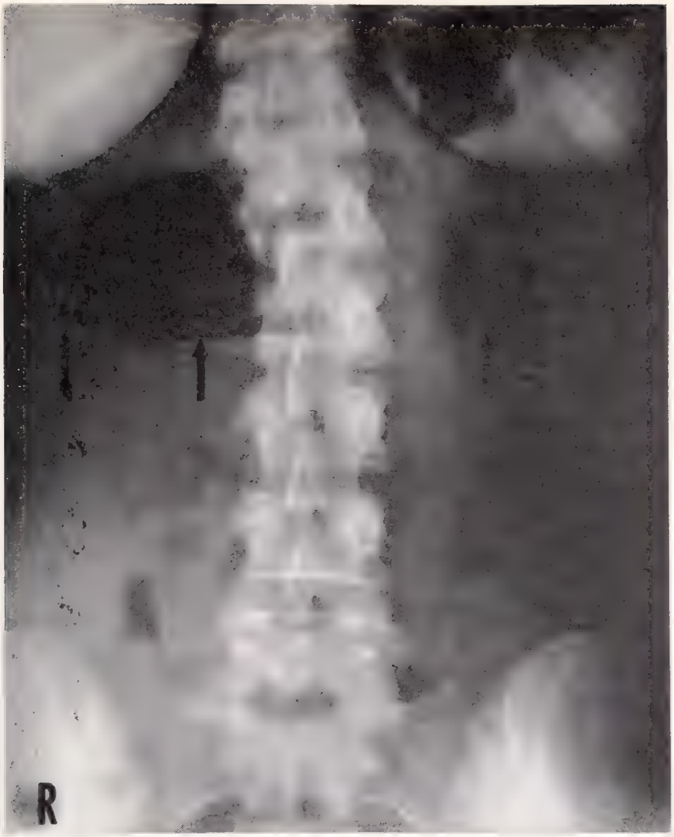
Case No. 356

A 35-year-old woman was admitted to the hospital with complaints of increasing abdominal pain and obstipation. History was within normal limits except for menstrual and bowel complaints. The patient reported severe menstrual pains throughout her life with gradual increase in painful periods over the last 5 years. She completed two successful pregnancies, the last one 7 years prior to admission; for one to two years following the pregnancy severe menstrual pains abated only to recur 5 years prior to admission. She also reported a chronic pattern of constipation requiring frequent laxatives which intensified during the periods. Her last period began one week prior to admission and was particularly painful in nature. Constipation proceeded to obstipation and there were no bowel movements for three days prior to admission. During this time, generalized abdominal pain developed and increased in severity. There was no fever. Numerous enemata were of no help; one of these produced some blood streaking but there was no spontaneous passage of blood per rectum.

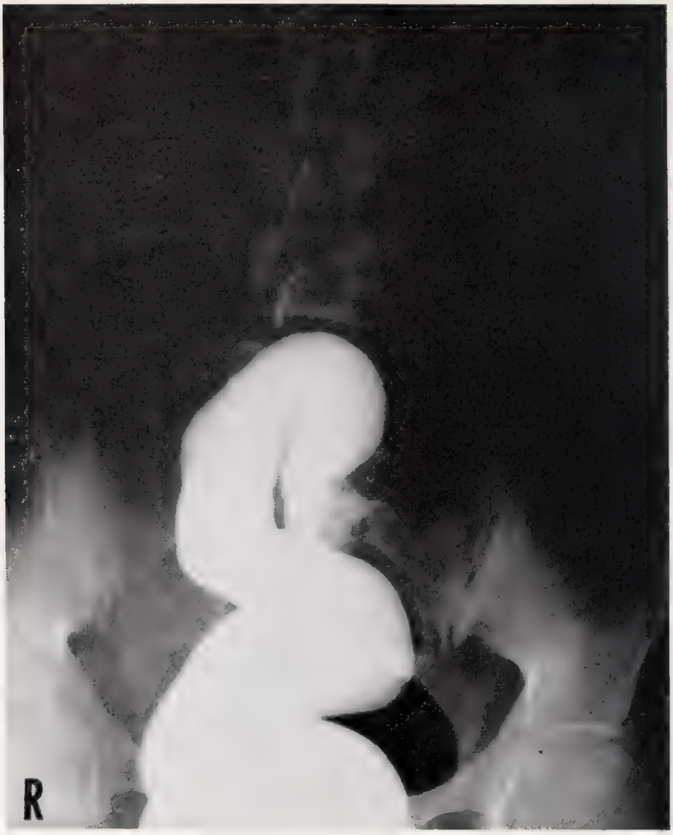
Physical examination of the abdomen revealed a diffusely tender, moderately distended abdomen. No specific mass was palpated. Pelvic examination revealed no abnormal finding. Radiographic study of the abdomen revealed findings pointing to a low, left-sided, colonic obstruction (Fig. 1). Barium enema



Case 356, Fig. 1. Erect postero-anterior film of the abdomen reveals broad fluid levels in the colon near the hepatic and splenic flexures (arrows). The fluid filled left colon, difficult to see in the reproduction, could be traced down to the pelvis but the rectum was empty. The diagnosis of a low left-sided colonic obstruction was therefore suggested.

examination was then performed (Figs. 2–4). A complete obstruction to the retrograde flow of barium was encountered in the distal sigmoid colon. The bowel showed some narrowing just distal to the site of obstruction with limitation of distensibility, and thickening and shirring of the mucosal folds. A definite ulceration was not delineated. A smooth indentation of the bowel suggested a submucosal component (Fig. 4).

The patient was explored. A hard mass in the sigmoid was palpated with surrounding induration. Frozen section revealed inflammatory changes. An anterior resection was performed. Careful exploration of the abdomen including the pelvic viscera revealed no other abnormality. The patient made a uneventful recovery. Menstrual periods after surgery are no longer particularly painful (four months) and bowel habits are now within normal limits.

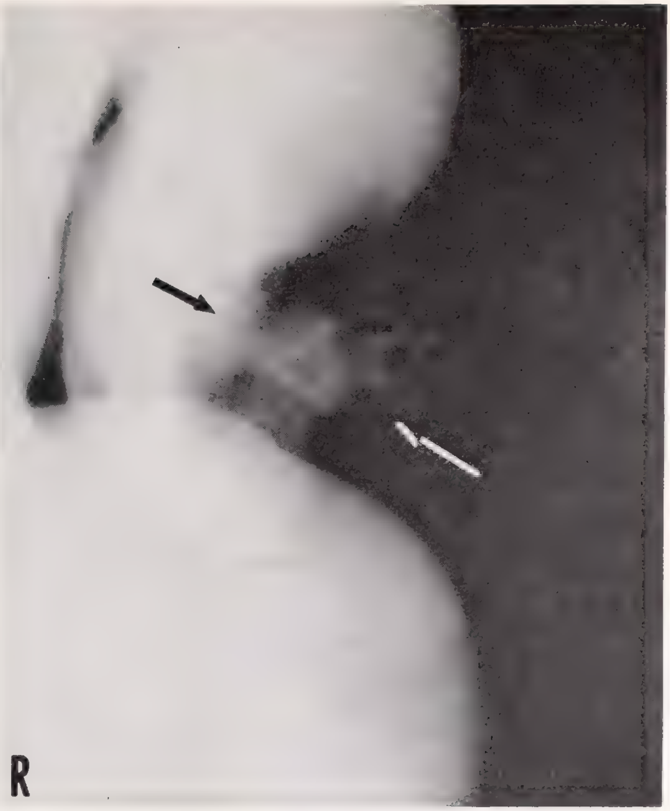


Case 356, Fig. 2. Postero-anterior film of the abdomen from barium enema examination shows a complete obstruction to the retrograde flow of barium in the distal sigmoid colon.

The Pathologist described a 19 cm length of sigmoid colon which was kinked in its midportion in relation to an area of induration and distortion measuring 6 cm in length. Upon opening the bowel, no mucosal lesion was identified. The bowel wall itself was markedly thickened measuring up to 2 cm in diameter. Histologic examination revealed foci of endometriosis with intact endometrial glands within the muscularis of the bowel, accompanied by fibrosis and inflammatory change. The final diagnosis was "segmental resection of sigmoid colon showing endometriosis with accompanying inflammatory stricture and obstruction."

Discussion

Endometriosis commonly involves the GI tract. About one-fourth of cases of endometriosis undergoing laparotomy will be found to have bowel involvement. The recto-sigmoid region is most frequently involved, apparently because of its close relationship to the uterus and adnexa. However, it is well to bear in mind



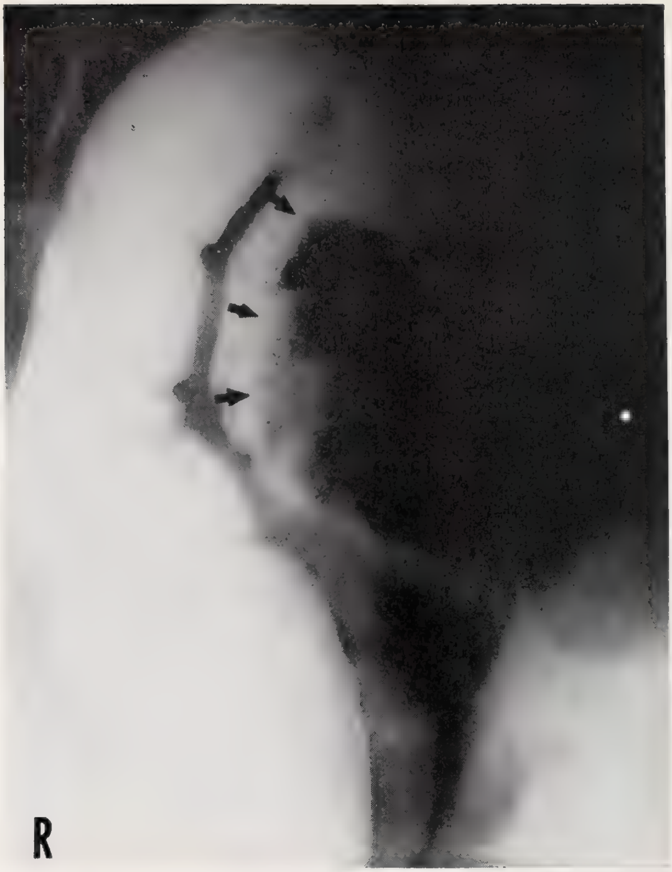
Case 356, Fig. 3. Spot film at the site of obstruction shows the transition between distensible bowel distally and the narrowed undistending bowel just distal to the point of obstruction. Here one notes thickneing and distortion of the mucosal folds and a suggestion of a shirring effect. A definite ulceration is not identified.

that endometriosis of the bowel can occur without any apparent involvement of the pelvic viscera. With symptomatic bowel involvement, partial obstruction is not uncommon, but complete obstruction is rather unusual (1–6).

Pathologically, the process usually involves the surface of the bowel and penetrates to involve the bowel wall. A cicatrizing effect in the wall is created due to the reaction to endometrial stroma and a mass is thus produced in a submucosal and intramural location. The fibrotic reaction also leads to distortion of the mucosal folds and often concomitant kinking of the bowel. The mucosa itself is rarely involved and mucosal ulceration would be unusual.

In the case presented the process was localized to the sigmoid colon and after a long history finally led to complete bowel obstruction. It seems likely that the painful periods were caused by crampy bowel pain rather than crampy uterine pain and thus far the postoperative course has been gratifying.

In addition to the complete obstruction, the roentgen features included dem-



Case 356, Fig. 4. Right anterior oblique 45 degree tilt-down view of the sigmoid shows another view of the point of obstruction, and this time there is evidence of a smooth convex indentation into the barium column (arrows) indicating a submucosal component. In addition to endometriosis, differential diagnosis should include metastatic carcinoma, primary carcinoma with submucosal extension and inflammatory sigmoiditis.

onstration of the submucosal mass effect and the distorted mucosal pattern. The mass in this case is larger than usually seen. Differential diagnosis should include metastatic carcinoma such as from the ovary or GI tract, primary carcinoma of the colon which has extended submucosally and through the wall distal to the primary site, and inflammatory sigmoiditis such as that due to diverticulitis or foreign-body perforation. The roentgen features are also reminiscent of those of carcinoid tumor as it involves the small intestine.

Case Report: Endometriosis localized to the sigmoid colon with complete obstruction.

Acknowledgment

This case is presented through the courtesy of Dr. John Arrigo, Good Samaritan Hospital, Suffern, N.Y.

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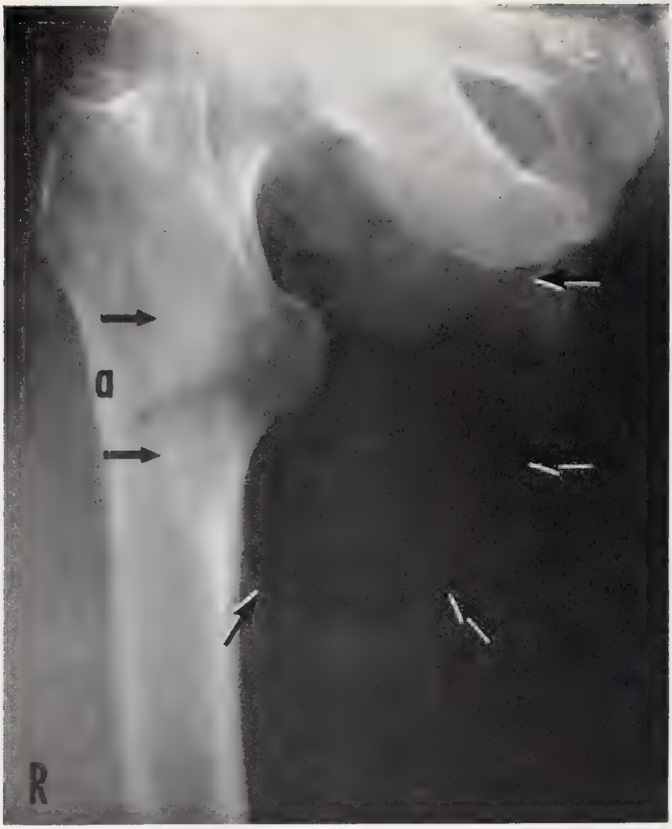
Case No. 357

An elderly man was referred for radiographic examination of the pelvis and right hip following trauma. The study revealed no evidence of fracture or dislocation. On the frontal and lateral views of the hip and upper femur (Figs. 1 and 2), there was noted a large ovoid radiolucent shadow located in the medial aspect of the thigh below the inguinal region. Since there was considerable calcification in the superficial femoral artery this vessel could be seen in relation to the radiolucent mass. It was displaced laterally and anteriorly and bowed by the mass in convex fashion. The diagnosis of an incarcerated femoral hernia was suggested, with fat in the hernial sac presumably omental in origin; there was no distinguishing feature to suggest a loop of bowel. The patient's referring physician was queried and he confirmed the presence of a femoral hernia from his records. Subsequent examination and history tended further to exclude the possibility of an incarcerated bowel loop in the hernia, but additional roentgen studies were not performed.

Discussion

The femoral sheath is an extension of the peritoneum of the abdominal cavity enclosing the femoral vessels. In effect, it represents a diverticulum of the peritoneum bearing some resemblance to a funnel flattened in the antero-posterior dimension. It is bounded by the inguineal ligament in front and the ileopsoas and pectineus muscles behind. Nerve, artery, and vein pierce the sheath from lateral to medial in that order, and medial to the vein there lies a small compartment which is termed the femoral canal (1). Thus a hernia entering the femoral canal is located medial to the femoral artery and vein (Fig. 1). The hernial sac can burrow along any of the tissue planes. In this case, it has displaced the superficial femoral artery laterally (Fig. 1) and has tunneled



Case 357, Fig. 1. Antero-posterior film of the upper femur includes the inguinal region and the medial thigh. A large ovoid lucency is seen in the upper medial thigh (arrows). The superficial femoral artery, visualized because it is heavily calcified, is convex laterally and lies over the bone of the intertrochanteric region on the lateral aspect of the lucent shadow (arrows A). It is normally located just medial to the femur in this projection.

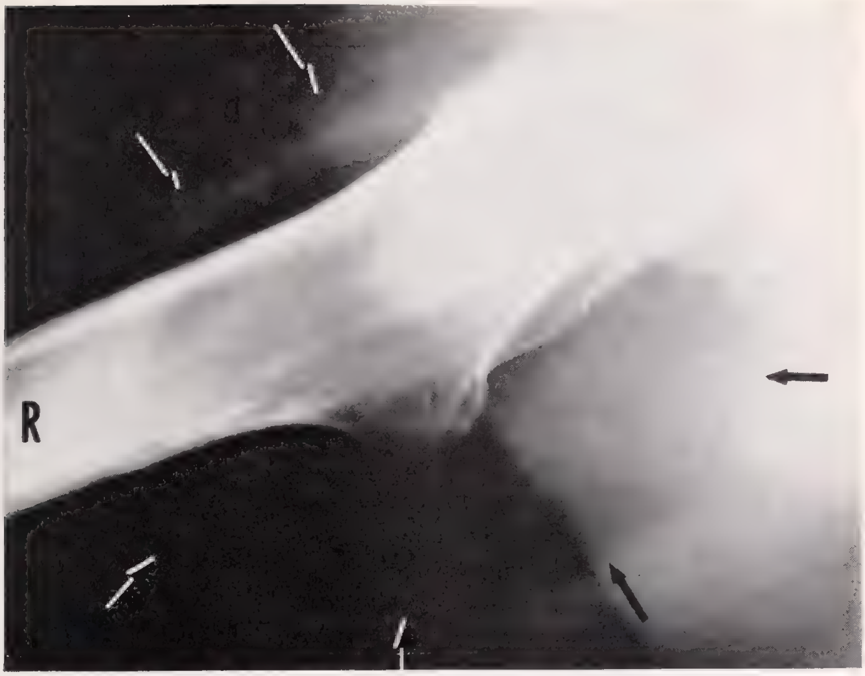
behind the artery thus creating an anterior convexity (Fig. 2). It has also extended postero-medially along the plane of the adductor muscles.

It seems likely on both roentgen and clinical grounds that the hernial sac contains fat rather than bowel but the latter cannot be excluded with absolute certainty without appropriate gastrointestinal contrast studies.

Case Report: FEMORAL HERNIA CONTAINING OMENTAL FAT DISPLACING THE SUPERFICIAL FEMORAL ARTERY.

Acknowledgment

This case is presented through the courtesy of Dr. Herman Wolf, Good Samaritan Hospital, Suffern, New York.



Case 357, Fig. 2. Lateral view of the upper femur and thigh again shows the heavily calcified superficial femoral artery convex anteriorly (arrows A). The large lucent shadow lies on a plane posterior to the artery and femur (arrows).

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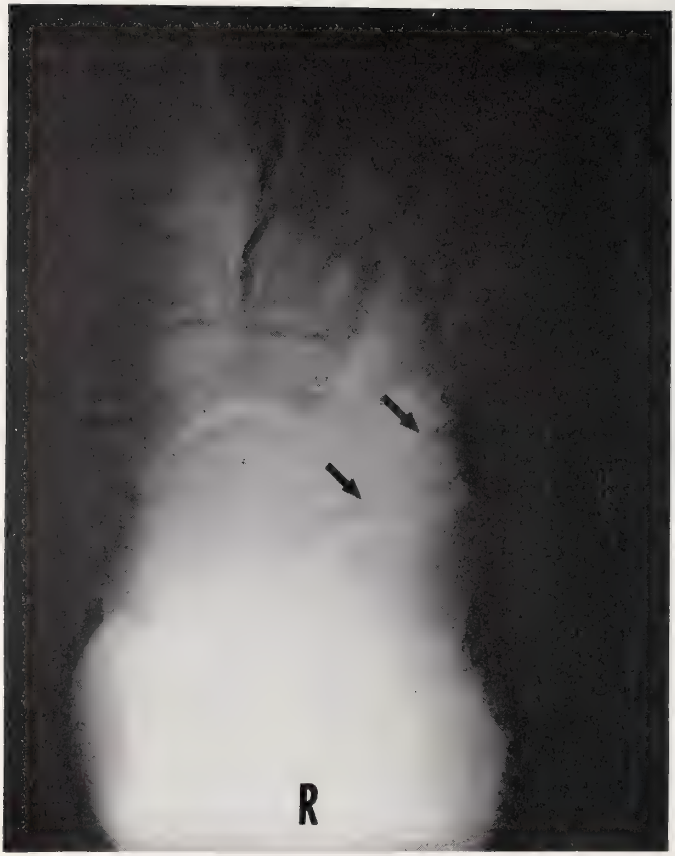
Case No. 358

A 24-year-old man complained of persistent pain in the right foot. The pain followed a series of recent sessions playing basketball. There was a history of previous foot pain following athletics during his teens.

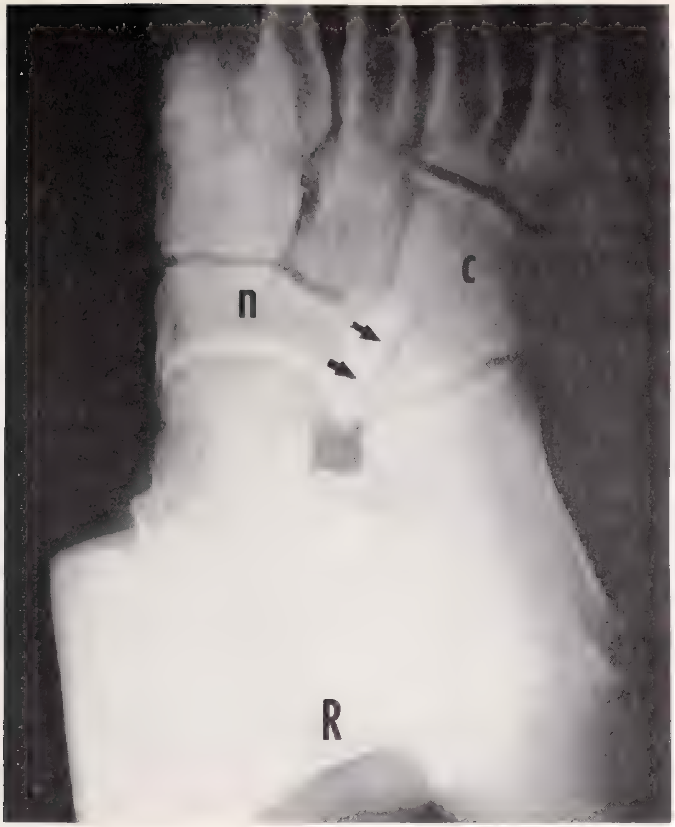
Clinical examination revealed pain and tenderness over the lateral peroneal area of the foot. The tarsal regions were asymmetric. On the right side there was a bony protuberance on the lateral aspect of the mid-tarsus not present on the left.

Radiographic examination was performed (Figs. 1, 2, and 3). A tarsal coalition was noted. There was bony fusion between the navicular and cuboid bones. There was an abnormal articulation between the calcaneous and the fused bony mass. A dorsal bony projection from the distal end of the calcaneous was noted at the abnormal joint.

A rigid molded arch was prescribed along with restricted activity. The patient's symptoms improved.



Case 358, Fig. 1. Antero-posterior view of the right hind foot shows an abnormal joint at the distal end of the calcaneus overlapping the junction of the navicular and cuboid (arrows).



Case 358, Fig. 2. Oblique view shows solid bony fusion between the navicular and cuboid bones (N.C.). Overlying the fusion there is seen a lucency; this represents an abnormal joint between the distal end of the calcaneus and the fused bony mass (arrows).

Discussion *

Tarsal coalitions are congenital abnormalities which usually are not discovered until adolescence at which time the patient presents with a "peroneal spastic flat foot". This is a syndrome consisting of pain over the lateral border of the foot radiating along the course of the peroneal tendons, resistence to inversion of the hind foot, and an awkward, flat-footed gait. Infections of the subtalar joint and rheumatoid arthritis are more rare causes of peroneal spastic flat foot, but most often the etiology is congenital tarsal coalition. The coalition may be bony or fibrous and may or may not be demonstrable by roentgenograms. The most common coalition is between the talus and the calcaneus and

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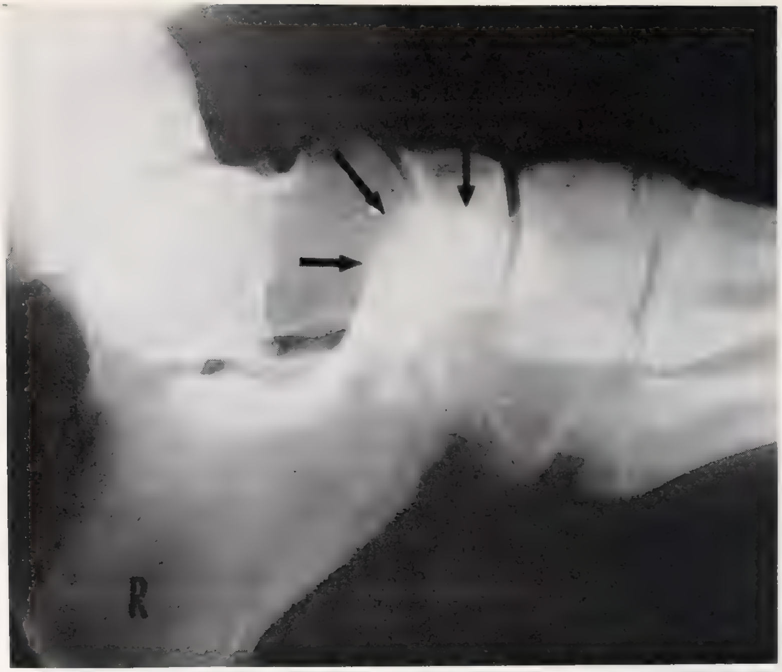
* Submitted by Joel B. Adler, M.D., Chief, Orthopedic Service, Good Samaritan Hospital, Suffern, N.Y. 10901.



Case 358, Fig. 3. Lateral view of the right hind foot reveals a dorsal projection of bone from the distal end of the calcaneus at the point of fusion and abnormal joint (arrows).

frequently requires posterior oblique views of the os calcis for demonstration. Calcaneo-naviculo-cuboid coalition is quite unusual.

An important roentgen finding which may explain the pathogenesis of the pain syndrome is lipping at the talo-navicular joint best seen on the dorsum on the lateral projection. This lipping or spurring is not prominent in this case at this time. The probable sequence is that the loss of mobility in one of the major tarsal joints over a period of many years causes excessive stress on the open mobile joints with resultant degenerative changes. Painful spasm in the peroneal tendons is a secondary effect.

Treatment of this condition, if mild, can be accomplished by rigid molded arch supports to help balance the foot and eliminate much of the subtalar motion. Triple arthrodesis may be necessary to effect relief in severe cases.

Case Report: TARSAL COALITION: CALCANEO-NAVICULO-CUBOID.

Guide for the Provisional Selection of Antibiotics

The appended table represents a computer-derived summary of the total experience of the antibiotic susceptibility of microorganisms isolated at The Mount Sinai Hospital during 1971. Its use as a guide for the provisional selection of antibiotics at this hospital until laboratory sensitivity determinations are made is obvious. By extrapolation, it may serve as a guide to the practicing physician elsewhere.

As a service to our readers, it is our intention to publish these findings annually as soon as they are compiled.

(Pending Laboratory Sensitivity Determinations)

COMPARATIVE ANTIBIOTIC SUSCEPTIBILITY OF MICROORGANISMS ISOLATED AT MSH IN 1971

Gram Positive Organisms	Drugs																	
	Ampicillin	Carbenicillin	Cephalothin (Keflin)	Chloramphenicol chloramycetin)	Erythromycin-Oleandomycin*	Gentamicin	Lincomycin	Neomycin-Kanamycin*	Novobiocin	Penicillin	Oxacillin (Prostaphlin) Methicillin (Staphcillin)*	Polymyxin-Colimycin*	Streptomycin	Tetracycline	Vancomycin	Sulfonamide	Nalidixic Acid (Neggram)**	Nitrofurantoin (Furandantin)**
Gram Positive Organisms																		
Staphylococcus aureus	4	—	1	2	2	2	1	1	1	4	1	—	—	2	1	3	—	—
Strept. fecalis (Enterococcus)	3	—	4	2	3	1	6	5	4	2	6	—	4	5	1	6	—	—
Beta hemolytic streptococcus	—	—	1	2	1	—	2	6	2	1	1	—	—	3	1	6	—	—
Streptococcus viridans	—	—	1	1	1	—	2	5	2	1	2	—	—	3	2	5	—	—
Diploc. pneumoniae (Pneumococcus)	—	—	1	1	1	—	1	—	2	1	1	—	—	2	1	3	—	—
Clost. perfringens (V. welchii)	1		1	2	2	5	2	6	5	1	2	—	—	2	2	5	—	—
Gram Negative Organisms																		
Esch. coli	3	2	2	2		1	—	2	—	—	—	2	3	3		4	1	1
Enterobacter (Aerobacter) aerogenes	5	2	5	3		1	—	2	—	—	—	3	3	4		4	2	2
Klebsiella species	5	5	2	3	—	1	L	2	—	—	—	2	2	4	—	5	2	2
Indole positive B. proteus	4	2	4	2	—	2	—	2	—	—	—	6	3	4	—	4	2	2
Proteus mirabilis	2	2	2	2	—	1	—	2	—	—	—	6	2	4	—	3	1	2
Ps. aeruginosa (B. pyocyaneus)	6	2	6	5	—	1	—	2	—	—	—	2	4	5	—	4	5	6
Pseudomonas sps.	5	3	4	4	—	2	—	2	—	—	—	2	4	5	—	4	3	2
Salmonella	2	1	2	1	—	1	—	2	—	—	—	2	3	3	—	—	1	1
Serratia marcescens	6	5	6	5	—	1	—	3	—	—	—	5	4	5	—	5	3	3
Shigella	2		2	1	—	2		1	—	—	—	1	2	2	—	—	—	—
Hemophilus influenzae	1	1	1	1	1	1	6	2	1	2	—	—	1	1	5	1	—	—
Mima herellea group	5	2	5	4	—	1	—	1	—	—	—	2	2	3	—	—	2	5

RATING FORMULA

1. over 95% strains susceptible.
2. 76-95% strins susceptible.
3. 60-75% strains susceptible.
4. 40-59% strains susceptible.
5. 10-39% strains susceptible.
6. less than 10% strains susceptible.

* Equivalent Spectra of Activity.
** Urinary Isolates only (Tested by Disk Agar Diffusion Method).
(—) Insufficient Number of Strains Tested.

Prepared by S. Stanley Schneierson, M. D., Director, Department of Microbiology, The Mount Sinai Hospital, New York, N. Y. 10029.

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In Memoriam

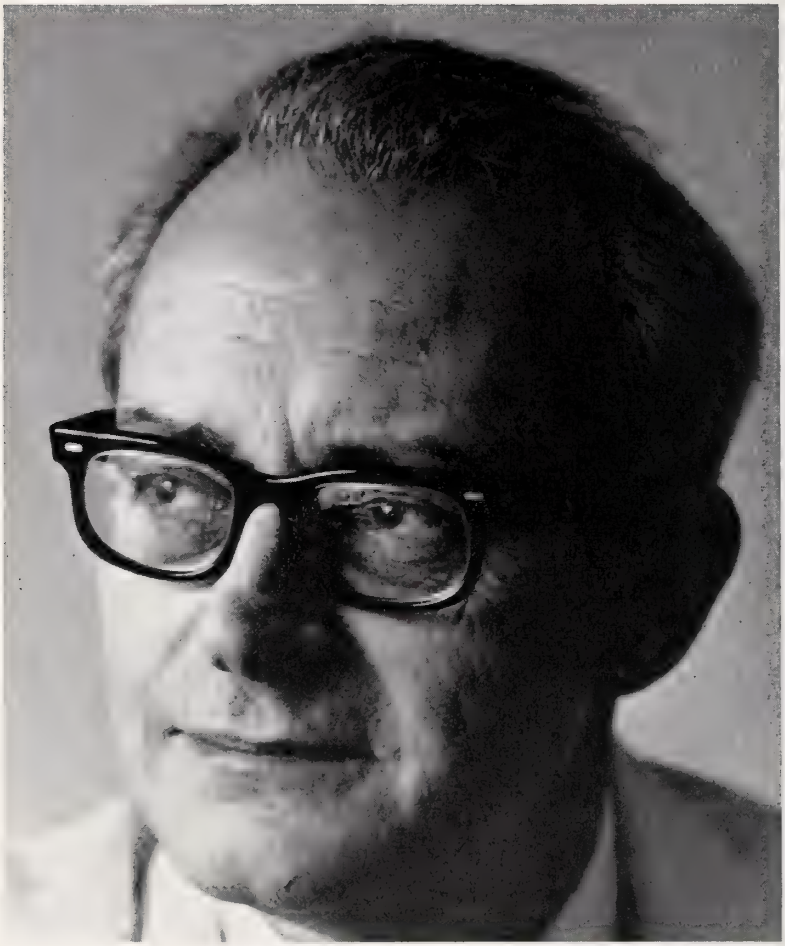
SOLOMON A. BERSON, M.D.
1918–1972

The death of Dr. Solomon Berson, Murray M. Rosenberg Professor of Medicine, at the age of 53, was a major personal and professional loss to the Mount Sinai and international scientific community. Dr. Berson came to Mount Sinai in 1968, at which time he had made, and was to continue to make, major contributions to virtually all segments of the disciplines of endocrinology and metabolism.

In 1956, Dr. Solomon Berson, in collaboration with Dr. Rosalyn Yalow, reported the heretofore unsuspected presence of insulin antibodies in patients receiving insulin. It became apparent to them that these observations could form the basis for the development of radioimmunoassay techniques. Utilizing this concept, they developed such a technique and used it to measure first bovine insulin and subsequently, with the development of sufficiently sensitive sera, human insulin. This radioimmunoassay technique is generally conceded to have opened new horizons, not only in the field of endocrinology, but in virtually all aspects of human biologic function in health and disease. Previous studies of peptide hormone secretion were seriously hampered either by the lack of or by the physiologic insensitivity of readily available bioassays. The radioimmunoassay technique provided the necessary specific and sensitive methodology for such studies.

Utilizing the basic principles of radioimmunoassay originally elucidated in the insulin studies, Drs. Berson and Yalow and their coworkers pioneered in the development of radioimmunoassay for other hormones, most notably growth hormone, ACTH, parathormone, and gastrin. In the course of these studies new information concerning the state of these hormones in plasma was obtained. Heterogeneity of immunochemical reactivity of plasma and gland parathormone was demonstrated as well as size and charge heterogeneity for plasma and tissue gastrins. Their most recent studies have presented evidence for the existence both in plasma and in pituitary gland extracts of at least two molecular species of ACTH. This has led to their suggestion that the hormone is produced and secreted from its site of origin in at least two forms, a finding which may be a general phenomenon in the secretion of many hormones. Other investigators have widely used the radioimmunoassay technique for measurement of an ever-increasing list of compounds (i.e., drugs, other peptide hormones, steroidal and nonsteroidal hormones, cyclic AMP, enzymes, and antigens), the study of which had been previously hampered because of lack of sufficiently sensitive and specific methodology.

The application of radioimmunoassay has led to new understanding of many areas of physiology and clinical medicine. Drs. Berson and Yalow's discovery of



SOLOMON A. BERSON, M.D.
1918–1972

the delayed, and sometimes heightened, insulin secretory response following administration of glucose to maturity-onset diabetics altered the concept that such diabetes was secondary to insulin lack, and has stimulated intensive investigation concerning the nature of the defect in such patients. Through further studies by their laboratory and others, it has also become evident that insulin secretion is responsive, not only to glucose administration, but to alterations in plasma concentrations of amino acids, free fatty acids, and gastrointestinal hormones, as well as to alpha and beta adrenergic stimulation of the pancreatic cell.

With regard to growth hormone, almost all of the presently available information on plasma growth hormone and growth hormone secretion has been obtained with the radioimmunoassay technique. The many studies of Drs. Berson and Yalow led to the concept that under conditions of carbohydrate deficiency, increased growth hormone secretion (with its resultant lipolytic action) provided an alternate metabolic fuel. Their observation of the lack of growth hormone responsiveness to hypoglycemia in hypopituitarism has clarified the diagnosis of various states of dwarfism, and has allowed for efficient use of the limited stores of human growth hormone available for therapy of growth hormone deficient dwarfism.

Solomon Berson's scientific achievements reveal only a fraction of his many brilliant talents. He had a wide knowledge of history and philosophy. He had an extraordinary knowledge of art and was a critic of unusual perception. He was a first-rate professional mathematician. In addition, he was a violinist of virtuoso quality, and it is certain that he would have had a successful career as a concert musician.

Dr. Berson was a man of genius of the first magnitude, but it is even more important to those of us who were his friends to make clear the greatness of his character. His great gift of friendship was based on his completely selfless concern for every human being around him. His interest in people was personal and direct, and it was in no sense an abstract feeling. Solomon Berson was a good and kind man. He was a person of principle who lived by a code of utmost rectitude, yet he was a most forgiving and understanding man. His judgment of others was always touched with great kindness and understanding.

Dr. Berson was an inspirational teacher of young people. Students from numerous countries came to work under his guidance. He leaves many scientific descendants who look upon him as their scientific father. He was a great leader of the house staff and young faculty members at Mount Sinai. These young men found in him an ideal leader, a moving teacher, and a pattern for their lives in medicine.

Solomon Berson was a great and wonderfully good man. We mourn his untimely death and are sad for the years which will pass without his presence among us. But, we are grateful that we had even a small share in his shining life.

DOROTHY KRIEGER, M.D. AND HORACE HODES, M.D.
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Paresis of Vertical Gaze in Basal Ganglia Disease

MORTON S. CORIN, ROBERT J. MONES, TERESITA S. ELIZAN, AND
MORRIS B. BENDER

This paper presents seven patients with severe paresis of vertical gaze and Parkinsonian features, discusses the relationship of these cases to classical Parkinson's disease and so-called progressive supranuclear palsy, and comments on their short-term response to L-dopa. Oculomotor function in basal ganglia disease is a subject which has received relatively little attention. Animal (1) and human (2 and 3) studies involving stimulation or ablation of basal ganglia areas have resulted in slight changes in oculomotor function. Occasional reports have appeared in the literature describing cases with varying basal ganglia syndromes with defective eye movements (4–6). In 1964, Steele, Richardson, and Olszewski (7) reported a group of patients with pseudobulbar palsy, dysarthria, dystonic rigidity of the neck and upper extremities, inconstant cerebellar and pyramidal signs, mild dementia, and supranuclear ophthalmoplegia affecting primarily vertical gaze. They argued for the separation of this syndrome, which they called progressive supranuclear palsy, from Parkinson's disease. In subsequent reports of this syndrome, however, many patients had prominent Parkinsonian features (8–11). The current view appears to be that the combination of oculomotor dysfunction, especially defective vertical gaze, and basal ganglia disease is seen in a small group of patients who have progressive supranuclear palsy. We have recently found oculomotor dysfunction to be quite common among patients with classic Parkinson's disease (12). There are also patients with Parkinsonian features who, in addition, have other signs of neurologic disease, including severe paresis of vertical gaze.

Case Material and Methods

The seven patients reported here were seen at The Mount Sinai Hospital, New York City, during the period of July 1969 to April 1970. Table I is a summary of their neurologic status on initial examination. All of them were examined specifically for oculomotor function in a format previously described for 70 patients with classic Parkinson's disease (12) with evaluation of gaze at a simple command, gaze on command to look at a specific target, gaze on command with visual gesture, gaze in pursuit of a moving target, optokinetic nystagmus (OKN), Bell's phenomenon, and oculocephalic maneuver with fixation. Eyelid and pupillary functions were evaluated as well. Electro-oculograms (EOG) were recorded for horizontal and vertical eye movements and head movement as previously described (13). Relevant photographs and movies were taken.

Case Reports

Case 1. This 53-year-old white woman was first admitted to the hospital on January 8, 1969 because of dizziness of three years' duration and inability to walk for three months due

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From the Department of Neurology,

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TABLE I

Neurologic Status of Patients on Initial Examination

Case Number	1	2	3	4	5	6	7
Age	53	71	79	68	62	85	66
Sex	F	F	M	M	F	F	M
Duration (years)	3	3	10	5	3	12	6
Bradykinesia	++	+++	+++	+++	++	+++	+++
Tremor	0	+	+++	++	++	+++	0
Face Rigidity	+++	+++	+++	+++	++	++	+++
Trunk Rigidity	+++	+++	+++	+++	++	++	++
Limb Rigidity	0	+++	+++	+++	0	++	0
Associated Movement	0	+++	+++	+++	++	+++	++
Retropulsion	+++	++	+++	+++	0	—	++
Organic Mental Syndrome	0	++	++	++	++	+++	++
Voice Change	+++	0	+++	+++	0	+++	+++
Pseudobulbar Features	++	++	++	++	++	+++	0
Motor Weakness	0	0	+	0	0	+	0
Babinski	yes	yes	no	yes	no	yes	no
Lateral Gaze	++	++	+++	++	++	++	+++
Upward Gaze	+++	+++	+++	+++	+++	+++	+++
Downward Gaze	++	+++	+++	+++	+++	+++	+++
Nystagmus	++	++	0	0	0	0	0
Pupillary Light Reflex	0	++	++	—	0	0	0
Convergence	++	+++	++	++	++	+++	+++
EOM Response to L-DOPA	yes	no	no	no	no	no	no

Legend: — = not tested
0 = no abnormality
+ = mild abnormality
++ = moderate abnormality
+++ = marked abnormality

to impaired equilibrium. She had difficulty going up and down stairs, and on bending would fall backwards, or occasionally, to her left or right. She was noted to have slowed down and was occasionally forgetful. She felt generally weak, had difficulty talking because of dryness of the mouth, and had noted double vision on right lateral gaze, sometimes even with one eye closed. On initial neurologic examination, mental status was normal. She had generalized bradykinesia. Walking was wobbly, short-stepped, occasionally punctuated by a few running steps forward. There was retropulsiveness and occasional falling to either side. Romberg's sign was positive. She had a stare, with infrequent blinking. There was some rigidity of the right arm and marked limitation of passive neck extension. Motor power, sensation, and deep tendon reflexes were normal. Rapid alternating movements were well performed, and associated thumb movements were preserved. No tremor was apparent. There was an equivocal extensor plantar response on the right. The pupils, fundi, and visual fields were unremarkable. Eye movements were full to command and pursuit, except that there was some impairment of downward gaze; in addition, when the head was flexed, there was some limitation of upward gaze. Optokinetic nystagmus was normal in the horizontal plane but absent in the vertical. There was unsustained nystagmus on right lateral gaze. Moderate blepharospasm was apparent. Cold water caloric testing in either ear elicited tonic deviation in the direction of the stimulus with nystagmus in the opposite direction. Bilateral stimultaneous stimulation with hot or cold water elicited no response, indicating defective vestibulo-ocular response in the vertical plane. Laboratory studies included an electroencephalogram, brain scan, lumbar puncture, and a left brachial arteriogram which were normal.

The patient was readmitted in August 1969. Examination was unchanged except that there was now almost total limitation of upward gaze, moderate limitation of downward gaze both to pursuit and command, with preservation of the downward response to oculocephalic maneuver with fixation. Horizontal gaze was somewhat jerky but otherwise unimpaired. Bilateral lid retraction was apparent. The voice was extremely high-pitched. There was slight impairment of mentation. The patient was started on L-dopa, and discharged on three grams daily. Subsequent clinic visits (latest May 28, 1970), revealed steady improvement in gaze with only a slight residual limitation of upward gaze. There was, however, an increase in bradykinesia and gait disability on L-dopa, 3.75 grams per day.

Case 2. This 71-year-old white woman was first seen on July 3, 1969 because of stiffness and unsteadiness of gait of two years' duration. There was a gradual onset of slowness of gait, unsteadiness, and difficulty getting in and out of chairs. She was noted to have a poor memory and to frequently fall backwards. Her handwriting had recently deteriorated and she had a peculiar stare. There was a long history of severe myopia. Neurologic examination showed unsteadiness of gait with a tendency to fall backwards. There was a mild rigidity of all extremities, but no tremor. Fine movements were slow and irregular. She was mildly confused. There was a marked stare with bilateral lid retraction, and marked limitation of upward gaze and convergence. Other eye movements were preserved. She was admitted to the hospital on November 24, 1969 with evidence of an organic mental syndrome and occasional episodes of unprovoked laughter. There was facial masking, rigidity of trunk and extremities, and generalized bradykinesia. There was a resting tremor of the hands, cogwheel rigidity of the neck and extremities, and bilateral extensor plantar responses. Visual acuity was limited to hand motion—O.S., and 2-/400 O.D., with correction. The fundi were normal. The pupils reacted sluggishly to light on an attempted convergence. There was a virtual absence of spontaneous eye movements including blinking, except for horizontal gaze. A moderate degree of blepharospasm was noted. There was a mild to moderate limitation and jerkiness of lateral gaze to command and pursuit (Figs. 1 and 2). Nystagmus was apparent on left

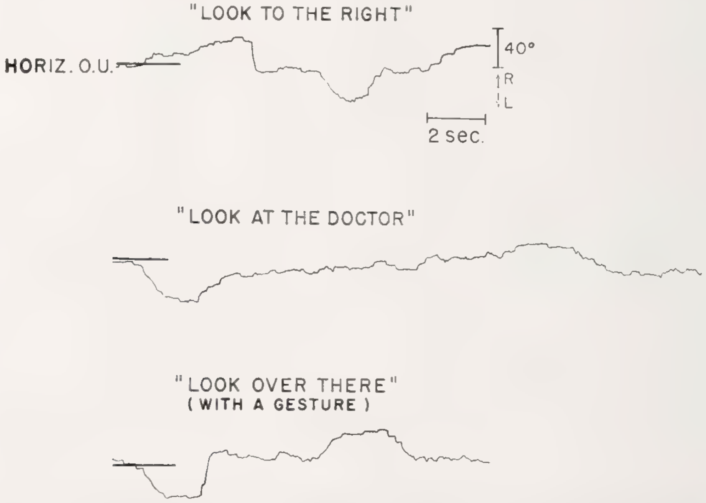

Fig. 1. Electro-oculogram (EOG) of Case 2. There is marked slowness and jerkiness of movements to the right and left, which is slightly better on gaze with visual gesture than to simple command. For Figs. 1–5: The type of recording is indicated on the left (i.e., horizontal or vertical eye, head or target position), the bold horizontal line on the left indicates the neutral position. On the right is indicated the time scale, scale of eye, head or target movements, and direction of movement with respect to the neutral position, i.e., for horizontal testing upward deflections indicate movement to the right (R) of the neutral position, downward deflections indicate movement to the left (L). For vertical testing, the comparable deflections are up (U) and down (D).

lateral gaze. Vertical gaze was absent (Fig. 3). Oculocephalic maneuver with fixation was normal to the left, right, and down, but there was no upward movement of the eyes (Fig. 4). Bell's phenomenon was absent. On OKN stimulation with a moving tape measure, there were very small, irregular beats horizontally, but no response vertically (Fig. 5). Cold caloric stimulation of either ear revealed normal horizontal ocular responses, but no response on bilateral simultaneous stimulation, indicating defective vestibulo-ocular response in the vertical plane. Routine laboratory studies including lumbar puncture were normal. The EEG revealed bilateral bursts of 2 to 3 cycles per second activity. A pneumoencephalogram showed dilatation of both lateral and third ventricles and of the basal cisterns. The patient was started on L-dopa and maintained on 3.0 grams daily. There was some improvement in the bradykinesia, but the unsteadiness persisted and there was no change in her eye movements when last seen on March 24, 1970.

Case 3. This 79-year-old white man was admitted to the hospital on October 16, 1969 because of increasing difficulty with walking and tremor of both hands of eight to ten years' duration. He had recently slowed down, had difficulty with fine hand movements, and had to be led in walking and turning. His speech had become more subdued and for two weeks he had difficulty in reading. For four days, he had shown personality changes, being extremely irascible. He had been irregularly on Parsidol® and Artane®, of uncertain dosages. General examination was unremarkable except for the presence of atrial fibrillation and a grade V/VI apical systolic murmur. On neurologic examination, he showed marked bradykinesia. He stood with the head and trunk bent forward and had to be led about. Severe retropulsion and shuffling of gait were noted. There was marked rigidity of trunk, neck, and extremities, and a prominent tremor of both hands and the right leg, with loss of associated movements. Power was only slightly impaired generally, and the deep tendon reflexes and plantar responses were normal. Rapid alternating movements were tremulous and performed with

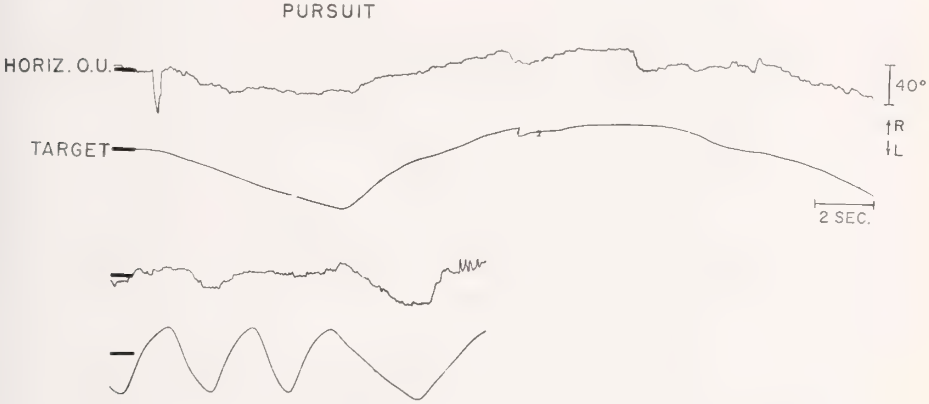

FIG. 2. Same patient as in Fig. 1. Poor horizontal pursuit is demonstrated.

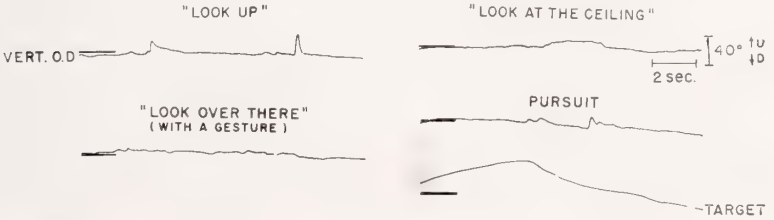

FIG. 3. Same patient as Fig. 1. Very little eye movement in the vertical plane is noted. A few blink artifacts are present.

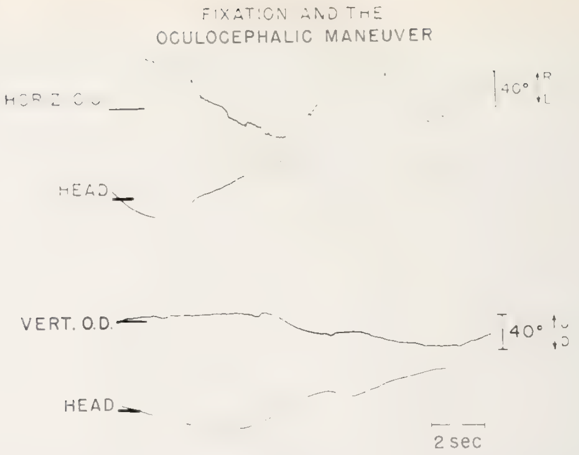

FIG. 4. Same patient as in Fig. 1. Oculocephalic maneuver with fixation produces greater extent of eye than head movement in horizontal plane, although eye movement is very jerky. There is little movement in the vertical plane, with more marked limitation of upward eye movements.

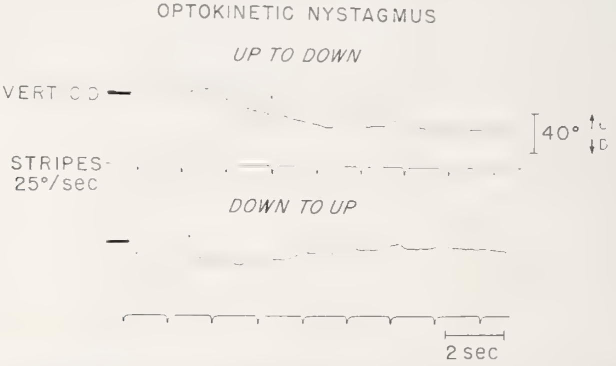

FIG. 5. Same patient as in Fig. 1. Note few nystagmoid beats and some following but none above the vertical meridian.

small excursions. Voice was almost inaudible. Mental status was essentially normal. Gag reflexes were mildly depressed. Visual acuity was 20/50 + 2 bilaterally, with correction. The fundi and visual fields were normal. The pupils reacted sluggishly to light and on attempted convergence. Ocular gaze to command was almost totally absent, with only a few degrees of lateral gaze and with head moving before eyes in all directions. On visual pursuit, horizontal gaze was almost full although saccadic, but vertical gaze was absent, although the head moved backward. On passive or active head movements in the vertical plane during visual fixation (oculocephalic maneuver), there was no upward movement of the eyes, but there was a small degree of downward movement. OKN was normal in the horizontal plane; in the vertical plane, there were a few beats downward but none upwards, and pursuit with targets from down to up was absent. Bell's phenomenon was only a slight upward movement. A moderate degree of blepharospasm and slight bilateral ptosis were apparent. Routine laboratory studies were within normal limits. The patient was placed on L-dopa with a maximum daily dosage of four grams. No change in his condition was apparent after six weeks on the dosage.

Case 4. This 68-year-old white man was admitted to the hospital on November 28, 1969 because of increasing difficulties with walking of five years duration. For three years he had had increasing stiffness, infrequent blinking, difficulty swallowing, and urinary retention. For one year he walked with small steps and only with great difficulty, necessitating assistance. There was a tremor of both legs and poor performance of fine movements. His expression had become fixed and he had a marked stare. His voice had become subdued and for approximately one year he was noted to be forgetful. On examination, he had markedly fixed facies with very infrequent blinking. There was almost total rigidity involving trunk and extremities with marked bradykinesia. He walked with assistance, had very small steps, a markedly stooped posture, retropulsiveness, and loss of associated movements. Motor power, deep tendon reflexes and plantar responses were normal. Alternating movements of all extremities were small and tremulous. Memory and orientation were mildly impaired but the rest of the mental status was relatively normal. Visual acuity, fundi, and visual fields were not remarkable. Pupillary evaluation was impossible because of previous cataract operations and glaucoma. There was a slight degree of bilateral ptosis and moderate blepharospasm. Gaze to command was full but saccadic in the horizontal plane and head movement preceded eye movement. In the vertical plane, there was some head movement, but no spontaneous or command eye movement. On pursuit, there was full horizontal gaze, slight limitation of downward gaze and a marked limitation of upward gaze. OKN induced by a moving tape measure was normal horizontally, but there was no vertical response except for a slight degree of following in the direction of the targets, both down and up. Oculocephalic maneuver with fixation elicited a normal range of eye movements with the exception of a moderate upward limitation. Bell's phenomenon was absent. Convergence was markedly limited. Routine laboratory studies including EEG and lumbar puncture were normal. He was started on L-dopa and maintained on three grams per day following hospital discharge on December 16, 1969. He was seen again on February 5, 1970 and April 23, 1970 when definite improvement in gait, speech, and rigidity was apparent. Extraocular movements, however, were worse, with increasing limitation of downward gaze on 3.75 grams of L-dopa daily.

Case 5. This 62-year-old white woman was admitted to the hospital on July 9, 1969 because of a three-year history of slowness of movement and increasing difficulty in getting in and out of chairs, walking, and turning around. She had great difficulty with fine hand movements. For one year, she had noted difficulty looking in any direction. She had to move her head either up or down to look in the desired direction. Examination revealed generalized bradykinesia, with an almost total absence of spontaneous blink. Gait was broad-based, slow, and unsteady, but strides were fair-sized. There was a loss of associated thumb but not arm movements. Motor power, sensation, and deep tendon reflexes were normal, and plantar responses were flexor. Facial and tongue movements were slow. There was a slight but definite tremor of the right hand. There was rigidity of the neck and trunk. On attempted vertical gaze, the head moved in the desired direction but the eyes remained stationary in the orbits. There were minimal vertical eye movements on pursuit. Lateral gaze was full but jerky, slowly performed and poorly maintained. Convergence was only slight. OKN could not be induced in the vertical plane; in the horizontal and oblique planes, the induced nystagmus beats were irregular and decreased in amplitude. Oculocephalic maneuver in the vertical plane during visual fixation resulted in a moderate degree of vertical eye movements. Lumbar puncture and bilateral brachial angiograms were normal. EEG revealed numerous bursts of delta activity in both temporal regions. The patient was discharged on L-dopa and maintained on 4.5 to 6.0 grams daily. She was reexamined on December 23, 1969; March 17, 1970; May 14, 1970; August 4, 1970; October 29, 1970; March 11, 1971; and May 13, 1971, and had shown no improvement in any sphere. She was noted to have developed a mild organic mental syndrome, and experienced frequent unprovoked crying spells; oculomotor dysfunction remained stationary. A six-month trial without L-dopa had not made any clinical difference.

Case 6. This 85-year-old white woman was admitted to the hospital on April 18, 1970 because of a progressive slowing down of twelve years duration. She had been bedridden for three years. A tremor of both hands had been present for seven to eight years and of the legs for an unknown period. She had recently become very forgetful and incontinent of urine. General physical examination revealed a grade V/VI blowing apical systolic murmur. She was oriented and alert but memory, calculations, spelling, and reversals were poor. Face-hand test was positive. There were frequent outbursts of unprovoked crying or laughter. Voice was low pitched. There was marked bradykinesia, and severe, generalized rigidity, more prominent in the trunk than in the extremities. She had mild generalized weakness. Walking was impossible except with assistance, at which times she maintained a simian posture with neck rigidly extended. There was a mild tremor of all extremities. Deep tendon reflexes were normal; there was a left extensor plantar response. Visual acuity, fundi, and visual fields were normal. Pupillary light reflexes were normal, but reactions were sluggish on attempted convergence, which was limited. There was impairment of horizontal gaze to command, with head movement preceding eye movements. There was greater defect of ocular gaze in the vertical plane; on command there was head movement in the desired direction but the eyes moved in the opposite direction relative to the head then back to the midline (Fig. 6). On pursuit, horizontal gaze was full, downward gaze was mildly limited and upward gaze was markedly limited (Fig. 7). On oculocephalic maneuver with fixation, there was a slight degree of upward movement only; eye movements in all other directions were full. OKN was reduced in amplitude in both horizontal directions, and in the vertical plane there was a minimal degree of following, but no nystagmus. Bell's phenomenon was absent. Laboratory studies including EEG, brain scan and lumbar puncture were normal. She was started on L-dopa and maintained on 3.5 grams daily after discharge on May 12, 1970. After four weeks, there was mild improvement in the bradykinesia and rigidity, but other parameters, including eye movements, were unchanged.

Case 7. This 66-year-old black man was admitted to the hospital on April 1, 1969 because of poor vision in the past two years, and difficulty with gait of five months' duration. Six years prior to admission, a change in the patient's voice had been noted, and speech had become stuttering, softer, and high-pitched. His wife noted a gradual deterioration in his mental state. General physical examination was within normal limits. His appearance was apathetic and lethargic, and he answered in a subdued high-pitched voice. He had echolalia and palilalia. He knew the month and year, and could name the President of the United States, but more detailed questioning of this type elicited no response. Calculations were poor; spelling and reversals, fair. There was infrequent blinking, fixed facies, and paucity and slowness of all movements. His head was protruded forward. Gait was unsteady with short shuffling steps, and a tendency toward retropulsion and propulsion; turning was poor. Associated arm and thumb movements were impaired. There was no motor weakness, and muscle tone was normal throughout, except for marked neck rigidity. Deep tendon reflexes were normal in the upper extremities, absent in the lower extremities. Plantar responses were flexor. Sensation was intact. Visual acuity was 20/20, bilaterally, with correction. Visual fields were full; fundi were normal. The pupils were moderately constricted but equal and reactive to direct and consensual light. When asked to look up, the head moved up and the lids moved slightly down, but the eyes did not move at all. On command to look down, the head moved slightly down and there was slight eyelid retraction, but no eye movement ensued. On command to look at the ceiling, the eyelids retracted and the eyes moved very slightly above the horizontal meridian. On command to look at the floor, the eyelids retracted and the globes moved slightly below the horizontal meridian. When looking at a target on his left or right, horizontal eye movements were better, but incomplete and irregular. With commands and gesturing, for eyes to move in a given direction, there was no improvement in gaze. On visual pursuit, the only movement was in the horizontal plane which was incomplete and irregular. On head movement during visual fixation, there was good relative movement of the eyes to the left and right, slight movement upward with eyelid retraction, and some movement downward. OKN was absent in all meridians. During strong eyelid closure, the eyes did not move upward as expected. Convergence was absent. Unilateral caloric testing (cold) elicited slight degrees of horizontal nystagmus to the contralateral side, which was interpreted as a poor response. Bilateral caloric vestibular stimu-

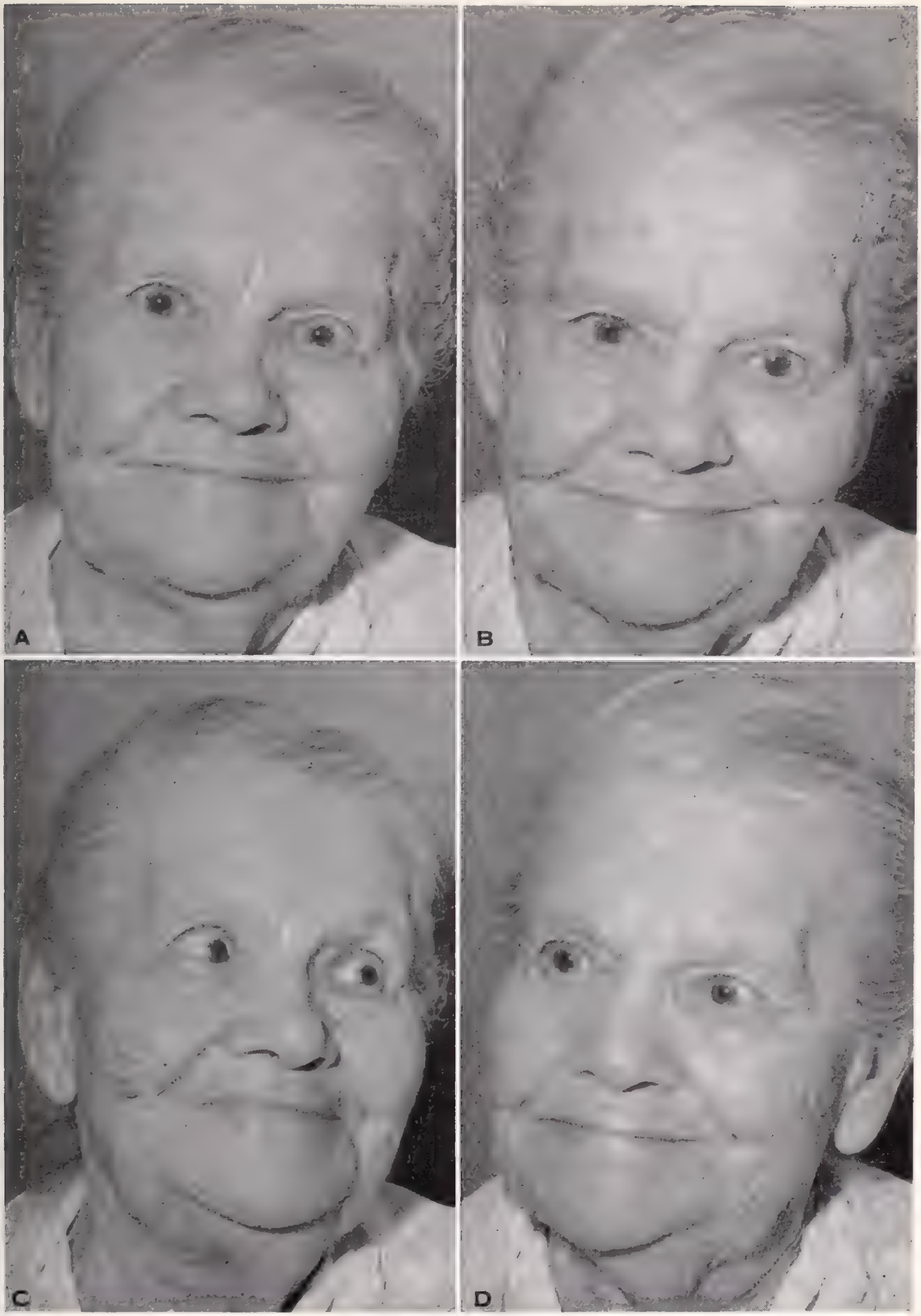

FIG. 6. Patient 6 with gaze to command (A) up, (B) down, (C) left, and (D) right. Of note is the virtual absence of upward gaze and rather marked limitation of downward gaze. Lateral gaze is somewhat better but not completely full.

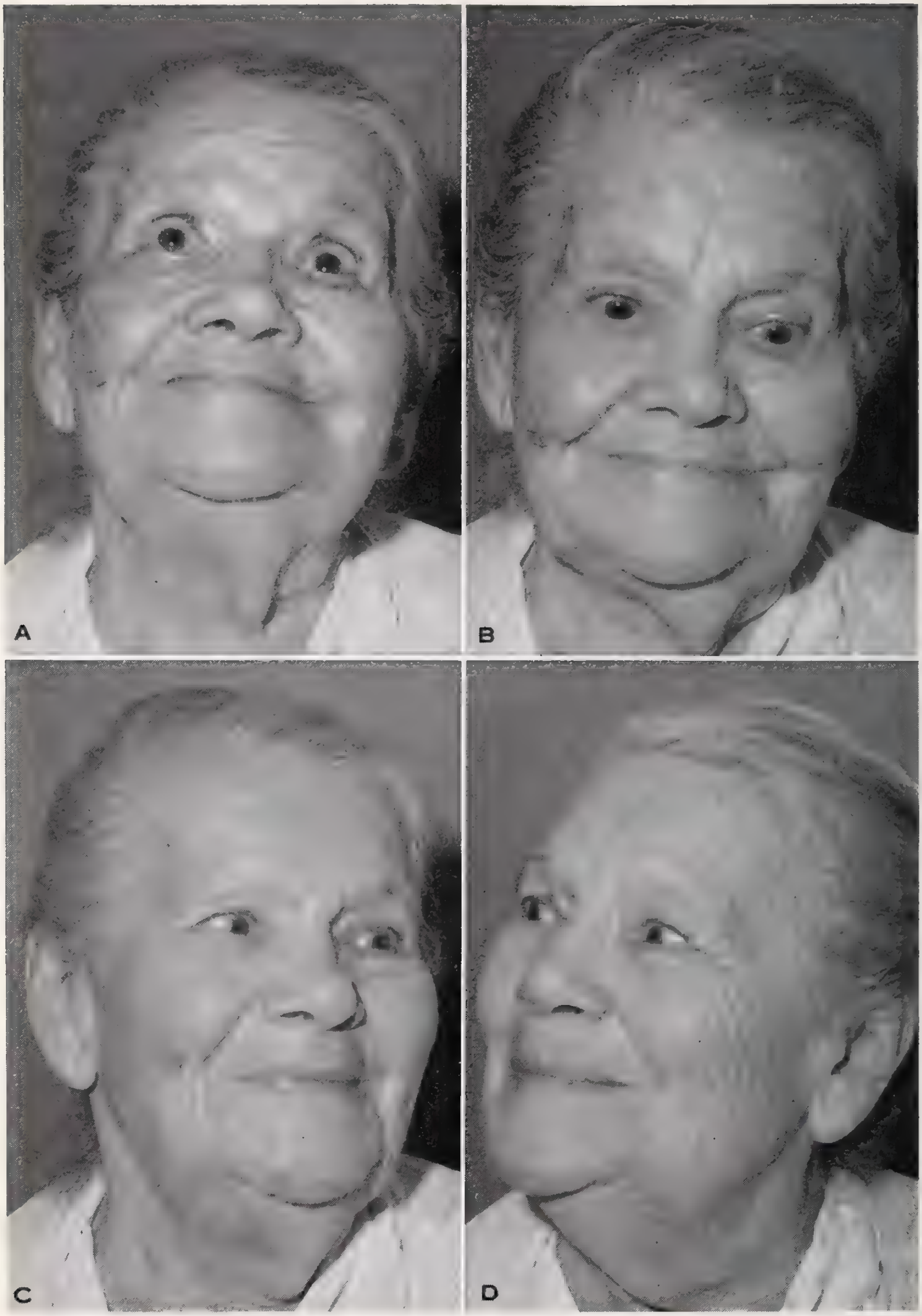

Fig. 7. Patient 6 with gaze on visual pursuit (A) up, (B) down, (C) left, and (D) right. In (A), head moves up, but eyes remain in same position relative to the head. Downward gaze is moderately limited and lateral gaze is full.

lation failed to elicit any response. Routine laboratory studies were unremarkable, as were skull x-rays, lumbar puncture, EEG, brain scan, pneumoencephalogram, and right brachial angiogram. He was started on L-dopa on April 14, 1969 with a maximal daily dosage of 7.25 grams. Except for slight improvement in gait, his neurologic status remained unchanged. Abnormal liver chemistries were noted, and the drug was discontinued on May 10, 1969.

Discussion

Each of these seven patients had disorder in vertical gaze, usually worse on upward than on downward direction. The most prominent defect was on command to move the eyes in a given direction, less so on visual pursuit of a moving target, and least on head movement during visual fixation. In examination of oculomotor function, the concept of gradation of stimulus strength for eye movements is a useful one (12, 14). Ocular gaze to command is a weak stimulus, and thus, is a more sensitive method to detect impairment, while oculocephalic maneuver with visual fixation is a strong stimulus and less likely to elicit an abnormal response unless the dysfunction is quite severe.

As part of the oculomotor dysfunction in the vertical plane, vertical optokinetic nystagmus (OKN) was severely limited in all these patients; in addition, horizontal OKN was abnormal in many, with irregular beats or impaired nystagmus and pursuit in either or both directions. In our experience, such defects in OKN are indicative of gaze deficits reflecting a disorder within the oculomotor system, with no further localizing significance. Defects in horizontal gaze were detected in conjugate eye movements, such as limitation of extent of gaze, jerkiness of performance, difficulty in initiating or maintaining gaze, or dissociation between head and eye movement, with head preceding eye movement.

These seven patients had varying degrees of generalized bradykinesia, facial masking, trunk and limb rigidity with cogwheeling, impairment of associated movements, tendency to propulsion and retropulsion, and tremor of the extremities—indistinguishable from those found in classic Parkinson's disease. In addition, however, pseudobulbar features, dysarthria, organic mental syndrome and marked defects of conjugate gaze, especially in the vertical plane, were invariably present. Voice and speech changes were common; volume was markedly reduced, pitch was either abnormally low or peculiarly high, and articulation was generally slow and unclear.

In a concurrent study of 70 patients with classical Parkinson's disease who were examined specifically for several oculomotor functions (12), a surprisingly high percentage, 75 percent, showed varying degrees of impairment, qualitatively similar to the seven cases described in detail in the present report, with the most striking abnormalities being in vertical gaze (worse on upward gaze), and with a significant number having abnormalities in convergence, lid function and pupillary reaction. In 14 of these patients (20%), the oculomotor dysfunction was as severe as in any of the present seven cases. The later, however, have features indicating a much more diffuse involvement of the nervous system; in addition to the basal ganglia, there was clinical involvement of the diencephalon, brain stem, and cerebrum.

The syndrome of progressive supranuclear palsy as originally described by Steele, Richardson, and Olszewski (7) differs from our cases in that such Parkinsonian features as tremor, limb rigidity, impaired associated movements and retropulsiveness were lacking. It was thought to be a fairly well delineated entity clinically and pathologically, with histologic lesions being diffusely scattered throughout the diencephalon, basal ganglia, and tegmentum of the brain stem involving the midline. Authors subsequent to Steele et al, however, have diagnosed this syndrome in patients with definite Parkinsonian features (8–11). It would appear that progressive supranuclear palsy is not an entity easily separable from Parkinson's disease. Alternatively, we might have to broaden the clinical concept of Parkinson's disease to include defects not generally thought of as being part of a lesion limited to the basal ganglia, such as pyramidal tract signs, pseudobulbar features, significant mentation changes, and defective conjugate gaze. The seven patients reported here show the overlapping features of two supposedly clear-cut clinical entities, with unequivocal dysfunction of the oculomotor system and the striate-nigral system.

Although we have no autopsy material, we can draw some conclusions from experimental data. It has been demonstrated that bilateral lesions, or lesions crossing the midline, at almost all levels of the brain, may result in vertical gaze deficits in the monkey. Those resulting from bilateral lesions of the prectectal-posterior commissure region are generally the most severe, and are frequently accompanied by convergence insufficiency, impaired pupillary reflexes, and lid retraction (15–18). Similar conclusions have been drawn from clinicopathologic studies in man. Lesions in this region have been reported in both Parkinson's disease (19) and progressive supranuclear palsy (7–11), although the degenerative process is generally more severe and widespread in the latter. The precise anatomic lesions responsible for vertical gaze defects in the cases presented in this report have yet to be demonstrated. A diffuse involvement affecting the basal ganglia, diencephalon, and paramedian zone of brain stem tegmentum may be expected.

The response to L-dopa of these seven patients is of some interest. Of ten recently reported cases of so-called progressive supranuclear palsy (20–27) many with Parkinsonian features, L-dopa therapy resulted in improvement in four, of whom only one showed some improvement in oculomotor function. Of our seven patients, two had moderate degrees of improvement in their general Parkinsonian status, and two had a mild improvement. One patient whose general condition actually worsened while on L-dopa, was the only one whose oculomotor function improved. All the others had unchanged oculomotor status. We have reported similar results with oculomotor deficits with short-term L-dopa trial in patients with classic Parkinsonism (12). We speculated that oculomotor deficits might be less sensitive to L-dopa than the usual tremor, rigidity, and akinesia, or that oculomotor deficits and the more generalized abnormalities are produced by different mechanisms.

Future studies suggested by this report would be pathologic data on dopamine concentration in the basal ganglia and brain stem nuclei, and cerebrospinal fluid data on homovanillic acid concentration in these and similar cases in comparison to that of classic Parkinson's disease and Steele-Richardson-Olszewski's syndrome.

Summary

Seven patients with marked limitation of vertical gaze and Parkinsonian rigidity, bradykinesia, and tremor are described. In addition, they had prominent abnormalities of voice, pseudobulbar features, organic mental syndromes, and pyramidal tract signs. These cases illustrate a most severe involvement of oculomotor functions. Less conspicuous oculomotor disturbances are found in other Parkinsonian patients. In the absence of pathologic studies, it is not possible to state whether the cases reported here are a variety either of Parkinson's disease or of the syndrome of progressive supranuclear palsy. On the other hand, they may represent a link in a spectrum between the two. It is unlikely that they will turn out to be pathologically distinct. Response of oculomotor dysfunction to L-dopa therapy was poor.

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The Absorption of Folic Acid in Man: Recent Progress

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This review will focus on recent developments in our knowledge of folic acid absorption. This is an area that has attracted much investigation over the past decade and there have been two excellent reviews (1, 2) on this subject in the past few years. A flurry of recent articles as well as our own studies on folate absorption will be discussed in the context of some general background. For more detailed background, the reader should refer to the above reviews.

Polyglutamate

Folic acid is a water soluble vitamin that exists in food mainly as pteroylglutamic acid in a conjugated polyglutamate form with seven glutamic acid molecules attached to pteroic acid (Fig. 1). In addition to being polyglutamic, it appears that the majority of food folate is in the reduced form as either 5- or 10-formyl tetrahydrofolate. The highest concentrations of folate are in yeast and liver, with appreciable amounts in vegetables and nuts. The average daily intake is about 700 μg, and the minimum daily requirement is between 50 and 70 μg.

Pteroylheptaglutamate is a large molecule, molecular weight 1215, and there is much evidence that it does not cross the intestinal membrane intact. Studies with everted sacs from rat jejunum have shown that polyglutamate on the mucosal side becomes monoglutamate (pteroylglutamic acid, PGA) on the serosal side (3). In vivo experiments with loops of canine small intestine perfused with polyglutamate demonstrated that only deconjugated folate reached the portal circulation (1, 4). Folate absorption in the dog after exposure of isolated intestinal segments to synthetic pteroylglutamates of various chain lengths has been studied by Baugh et al (4). They observed biologically active folate appearing in the mesenteric vein with pteroylmono-, di-, tri-, penta-, and heptaglutamate in the lumen. Generally the absorption rate was inversely related to the length of the gamma glutamyl side chain. Pteroylmonoglutamate was the predominant form entering the blood from each of the precursors tested. However they obtained evidence that pteroyldiglutamate may enter the mesenteric vein after placing pteroyldi- or triglutamate in the lumen but not with higher polyglutamates. In addition, selective radioactive labeling of the first glutamic acid molecule of polyglutamate orally administered in man (5) resulted in labeled monoglutamate in the plasma, while radioactive labeling of the second glutamate resulted in radioactivity being excreted as $^{14}CO_2$ by the lungs.

How polyglutamate becomes deconjugated to monoglutamate is not yet clear. Folate conjugase, the enzyme that hydrolyzes polyglutamate, is present in

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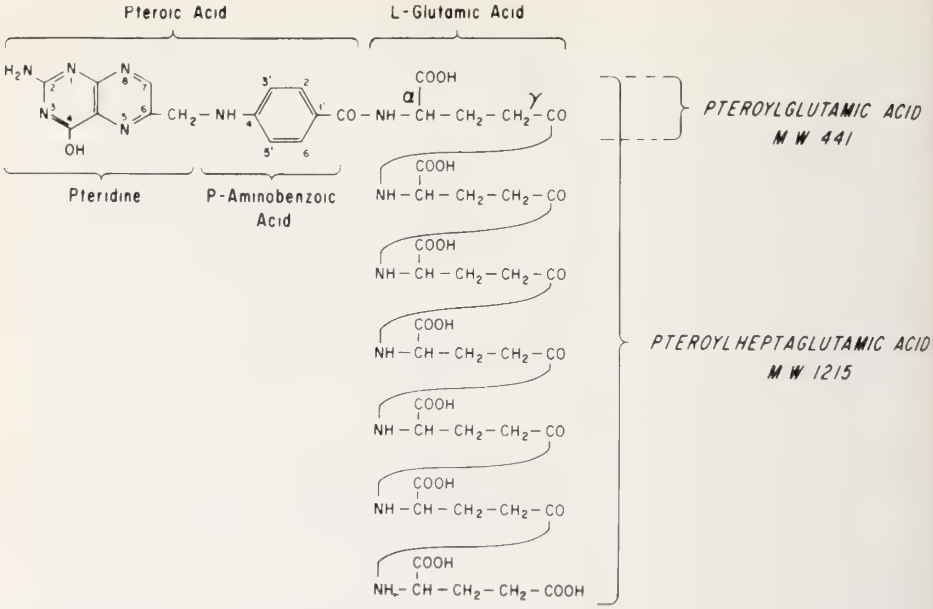

FIG. 1. Structure of pteroylglutamic acid in its polyglutamate form. (From Rosenberg, *et al* (2))

intestinal mucosal cells, primarily in the mitochondrial-lysosomal fraction (2, 6) and it appears most likely that this is where hydrolysis of the polyglutamate takes place. How the molecule reaches this part of the cell is not known. Bernstein and Gutstein (7) have measured an appreciable amount of folate conjugase in bile with optimal activity at pH 4 to 5, probably not significantly active at intrajejunal pH. Pratt and Cooper (8) were able to find only a much smaller amount of folate conjugase activity in bile, using the same pH, so this aspect, whether clinically significant or not, is still in dispute. In several studies of impaired polyglutamate absorption, in tropical sprue (9) and in diphenylhydantoin (DPH) administration (10, 11), there has been an attempt to correlate rate of absorption and folate conjugase assays of mucosal biopsies. In tropical sprue, the correlation was poor and in DPH, the results could not be confirmed by others (1, 12).

The rate of absorption of orally administered polyglutamate versus pteroylglutamic acid (PGA) is in dispute. One group has concluded that polyglutamate is only absorbed at one-third the rate of PGA (13) while another has found an equal urinary excretion rate from both forms of folate (2). The effect of disease or drug on polyglutamate versus PGA absorption is obviously effected by any basal differences in their rates of absorption so this question is an important one to answer. Several studies purporting to show impaired polyglutamate absorption hinge on this point.

Reduction and Methylation

There has been disagreement concerning the mode of transport of folate across the intestinal wall and the site of conversion to metabolically active

5-methyltetrahydrofolate. Baker et al (14) suggested that PGA was converted to 5-methyltetrahydrofolate during transport across the intestine. Using dihydrofolate and tetrahydrofolate administered orally and intravenously, Chanarin and Perry (15) also concluded that reduction and methylation of PGA occurred in the gut wall during its absorption. However, Whitehead and Cooper (16) found that orally given PGA appeared unaltered in portal blood and that its conversion to, and release as 5-methyltetrahydrofolate occurred in the liver. When Butterworth et al (5) gave ^{14}CPGA orally to one patient and could not demonstrate a rise in 5-methyltetrahydrofolate in peripheral blood and there was no change in the labeled folic acid, they assumed there was no conversion in the intestine.

Recently, Melikian et al (17) studied this problem extensively in eleven patients who had undergone portal or hepatic vein catheterization. Following an oral dose of PGA, they measured levels of folic acid and its metabolites, using microbiologic assays and tetrazolium bioautography, in blood samples obtained from portal, hepatic, and systemic veins. The ingested PGA appeared promptly in the portal blood with little or no increase in 5-methyltetrahydrofolate, indicating that PGA does not seem to be measurably reduced and methylated during absorption through the intestinal mucosa. With hepatic vein catheterization, there was an increase in 5-methyltetrahydrofolate in hepatic vein blood following oral PGA, implying the release or displacement of stored or recently formed 5-methyltetrahydrofolate from the liver. The enzyme dihydrofolic acid reductase reduces PGA to dihydrofolate very slowly at the physiologic pH of the body, but dihydrofolate is reduced quite rapidly to tetrahydrofolate, which is then methylated. Since most dietary folates are already in reduced form, reduction and methylation can occur rapidly and PGA is not usually found in systemic venous blood. Even when PGA alone was given to subjects in small amounts as used by Melikian et al, it was still not detected in systemic venous blood although present in moderate amounts in portal venous blood. This also lends support to the concept that reduction occurs mainly in the liver. It is probably relevant that the dihydrofolic acid reductase content of the liver is much higher than that of the intestine.

Pratt and Cooper (8) also performed detailed experiments designed to evaluate effect of orally ingested labeled PGA and of 5-formyl-tetrahydrofolate (folinic acid) on plasma and bile folate levels. They used microbiologic methods and radioactivity and found that a relatively large dose of ^{3}HPGA, 1 mg, resulted in a rise in free PGA in the plasma for about 30 minutes followed by a flushing into the plasma of 5-MTHF with peak level at 60 minutes, followed in turn by 5-MTHF derived from the ingested PGA. Folinic acid, already in reduced state, produced an earlier rise in 5-MTHF due to its more rapid transformation. These findings described the temporal relationships of the change in folic acid after absorption and are consistent with the liver, not the gut, being the main organ involved. In the study by Baugh et al (4) of polyglutamate absorption in canine small intestine loops, comparison of radioactivity and biologic activity gave no evidence of conversion to reduced or methylate forms during passage through the intestinal mucosa.

Thus, methylation and reduction appear to take place primarily in the liver, not in the gut, in contrast to deconjugation of polyglutamate which takes place in the gut.

Mode of Transport

Early studies on absorption of folic acid utilized only the monoglutamic form, PGA, because a reliable source of polyglutamate was not available and because PGA is the essential absorbed portion of the polyglutamate. In the late 1950's, Chanarin et al (18) devised a PGA oral tolerance test with folic acid serum levels and excretion in the urine measured microbiologically with L. casei. This test was useful for differentiating normals from grossly disturbed folate absorption, as in sprue, but required a large oral dose, 40 μg/kg, so it was not very sensitive. The same test was later made easier by using tritium-labeled PGA (^{3}HPGA) (19, 20) however the same problem existed. In addition, this technique did not tell us anything about where and how the folate was being absorbed and the problem of tissue saturation and metabolism, and renal function were added factors that could influence the results.

There were several early studies in rats dealing with the question of active versus passive PGA transport and location of absorption in the gut. These yielded conflicting results, with evidence for and against active transport or movement against a concentration gradient. One of us originally suggested that the apparent accumulation of PGA against a concentration gradient could be accounted for by the conversion of PGA to reduced folate by hamster jejunum (21). The predominant circulating and storage form of folate is 5-methyltetrahydrofolate. Moreover the principal dietary folate compounds are probably reduced forms of polyglutamate. Therefore, Strum et al (22) recently studied rat intestinal absorption of 5-MTHF in vitro using a synthetic highly purified radio labeled diastereoisomer. Chromatography confirmed that it was not altered after transfer from mucosa to serosa. Accumulation against a concentration gradient was not observed in duodenal, jejunal or ileal segments. Unidirectional transmural flux determination did not indicate a significant net flux. Mucosal to serosal transfer of 5-MTHF was similar in all segments of the small intestine. No alteration in 5-MTHF transfer was found in the presence of metabolic inhibitors or folate compounds. These results indicate that 5-MTHF is not absorbed by the rat small intestine by a carrier-mediated system and suggest that 5-MTHF transfer most likely represents diffusion.

A breakthrough in understanding folate absorption in the human gut was achieved by the advent of the intestinal perfusion technique. This allows study of absorption in the human by infusing a solution with a known concentration of PGA through a tube passed into the intestine and then collecting a sample of this solution from an additional tube placed distally. By this means, one can calculate disappearance from the intestinal lumen of PGA per unit time and distance and eliminate other organic factors. This technique was adapted to the study of PGA absorption by Hepner et al (23) with a double lumen tube. They studied several aspects of folate absorption; what part of the human intestine is

PGA absorbed from, is absorption active or passive, and what changes occur in coeliac sprue. They found that folate absorption is primarily in the proximal jejunum and negligible in the ileum and that folate absorption is markedly diminished in sprue. Their results suggested an active saturable transport process but their method of demonstrating this has been criticized.

We have also studied absorption of PGA with a perfusion system with several changes (24). We have been using a triple lumen tube which appears to be more accurate than a double lumen tube for technical reasons and we have used ^{3}HPGA rather than just PGA as we feel our quantitative results are more accurate. We have paid particular attention to the relationship of PGA absorption to absorption of sodium, water, and glucose. We perfused subjects with PGA in two different solutions, both isosmotic but one consisting of only saline while the other contained glucose, 55.6 mM, and saline. We found that there was a marked rise in PGA absorption during the glucose and saline perfusion (Fig. 2) while at the same time, there was a marked rise in water and sodium transport. The enhancing effect of glucose on water and sodium flow was previously known but out findings indicated that other solutes such as folic acid may also be effected. The explanation is probably due to a solvent drag effect secondary to water flow, a passive process, though our study did not conflict with an active mechanism as well.

Another recent study using rat everted sacs has confirmed our observation that glucose increases PGA transport and water transport in a parallel manner. Smith et al (25) also made some other interesting observations, that the PGA transport mechanism was associated with saturable kinetics, compatible with either active transport or facilitated diffusion but that there was no PGA transport against an electro-chemical gradient when mucosal and serosal PGA concentration were equal. This is strong evidence for passive transport. They also noted that PGA was optimally transported at pH 6.0–6.5 with a drop-off at pH 7. This has been applied in a study of humans (26) where it was suggested that PGA absorption may be impaired by conditions where intestinal pH is

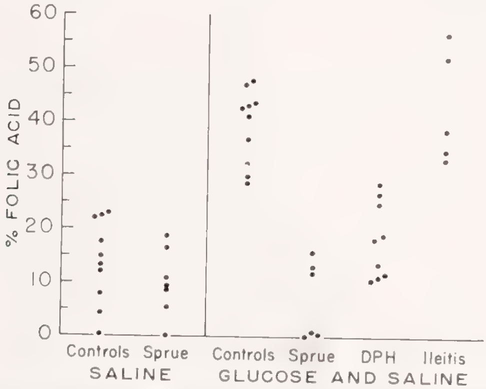

FIG. 2. Percentage absorption of folic acid as ^{3}HPGA from perfusion studies under various conditions.

elevated. Oral administration of sodium bicarbonate with PGA produced lower serum PGA levels than oral PGA alone. It was also claimed that intra-duodenal pH in epileptics on long-term diphenylhydantoin therapy was higher than in controls, possibly accounting for impaired PGA absorption but the pH change recorded was a very small magnitude.

Disease and Drugs

Our interest in relating PGA transport to sugar, salt and water absorption has been extended to a group of patients with sprue, both non-tropical and tropical (27). Using the same perfusion technique mentioned above, we found that PGA absorption from a saline solution was only mildly impaired compared to controls. However, when PGA was perfused in a glucose and saline solution, the increase in PGA absorption seen in controls did not occur and the impairment of folate transport became grossly evident (Fig. 2). Changes were more profound in non-tropical than in tropical sprue. Glucose, sodium, and water transport were also markedly abnormal with net secretion of water present in most patients, a finding previously described by Fordtran et al (28). We have performed similar studies in regional enteritis which have yielded normal results (29) (Fig. 2).

Another area of recent interest has been the effect of diphenylhydantoin (DPH) on folate absorption. The association of serum folate deficiency and long-term DPH therapy is well established. The explanation for this association has been debated. Several early studies (30, 31) measuring serum folate levels after oral folate administration suggested an inhibitory effect of DPH on PGA absorption. Then a series of studies (10, 11) were published stating that DPH inhibited absorption of polyglutamate rather than PGA and that DPH inhibited folate conjugase activity. These studies were made possible by the availability of relatively pure polyglutamate derived from a chromatographic separation of yeast. However, the evaluation of folate absorption was derived from serum levels after oral polyglutamate administration, an imprecise method, and several subsequent studies failed to show any inhibition of folate conjugase activity by DPH (1, 12).

We have recently studied the effect of DPH on PGA absorption, again utilizing the triple lumen tube perfusion technique. We demonstrated a clearcut and significant inhibitory effect, by adding DPH to our perfusing solution at a concentration below that attained intrajejunally after oral administration of DPH (Fig. 2). There were minor effects of DPH on sodium and water transport as well but inhibition of PGA transport appeared to be independent of changes in water and net sodium flow. Polyglutamate has not yet been studied in a perfusion system so any specific DPH effect on its transport remains in question. Reduced forms of folate have also not yet been studied by perfusion.

Actively drinking alcoholics are frequently folate deficient, often with a concomitantly reduced dietary intake of folate. However, decreased absorption of orally administered labeled folic acid has been previously shown by Halsted et al (33) by measuring plasma and urinary levels of radioactivity in a study of recently drinking alcoholics. These findings have been more recently extended (34) in binge-drinking alcoholics with normal hepatic function, utilizing the same triple lumen perfusion system with ^{3}HPGA described above. The patients with a good diet during their binge had normal absorption whereas those with a poor diet had significantly diminished absorption. Abstinence from ethanol and a hospital diet resulted in rapid improvement of ^{3}HPGA absorption. When ethanol was then refed to seven of these previously abstinent patients with a continued hospital diet, only two of them had diminution of their ^{3}HPGA uptake. The principal cause of limited PGA absorption during the drinking binge appears to be poor nutrition rather than a toxic effect of ethanol on the jejunum. Using the more pharmalogic oral PGA tolerance test, Lindenbaum et al (35) also were unable to show decreased folate absorption in controls fed ethanol over a prolonged period.

Although the majority of women on oral contraceptives can absorb sufficient folate from their food to avoid becoming deficient, it has been shown that women taking the "pill" have a lower average concentration of folate in the serum and red cells than do controls and occasionally folate deficiency with anemia develops, despite adequate diets. Streiff (36) has now shown that women on oral contraceptives absorb PGA as well as normal controls as measured by rise in serum folate levels. However, when polyglutamic folate was given orally, the absorption was decreased by approximately 50 per cent. Similar inhibition of folate polyglutamate absorption but not of PGA by oral contraceptives was also found by Necheles and Snyder, also measuring rise in serum folate (37). Though the evaluation of absorption was indirect, it seems possible that there is an effect of oral contraceptives on the enzymatic deconjugation of polyglutamic folate, resulting in inhibited absorption.

Thus, in the past few years, our knowledge of the events taking place during transport of folate has advanced considerably. The possible significance of impaired deconjugation of polyglutamate in disease states or in association with pharmacologic agents is only one of many intriguing aspects of this subject still to be explored.

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Studies on Blood Coagulation

I. The Influence of AHG Concentrate on the Activity of Antithrombin III in Normal and Hemophilic Serum

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Abstract

The addition of antihemophilic globulin (AHG) concentrate to normal or hemophilic serum was found to lower the antithrombin-III activity of the serum. The inhibitor activity was diminished by dialysis of the serum against physiological saline, lowered by heating at 56°C, and was abolished by extraction of the serum with diethyl ether. No proteolytic (tryptic, chymotryptic) or esteratic activity was demonstrable on addition of the AHG concentrate to normal or hemophilic serum. The observed decrease in the antithrombin III activity in serum on addition of AHG concentrate could not be attributed to proteolysis of the inhibitor nor to activation of residual prothrombin.

Cooperberg and Teitelbaum (1) observed that the activity of antihemophilic globulin (AHG) is higher and antithrombin-III activity is lower than normal in the plasma of patients with coronary disease. Teitelbaum et al (2) observed elevation of AHG and lowering of antithrombin activity in rats fed a thrombogenic diet.

On the conjecture that the observed inverse relationship between AHG and antithrombin-III activities may be a general phenomenon, one would expect that antithrombin-III activity should be increased in the Type A hemophiliac. Von Kaulla and von Kaulla (3) reported antithrombin-III activity to be higher than normal in patients with hemophilia A, and lower than normal in patients with coronary disease. They showed further that elevated antithrombin-III activity in the hemophiliac was independent of the rate of thrombin generation. Miles, von Kaulla and von Kaulla (4) suggested that the hemostatic action of AHG concentrate might be related to neutralization of an "inhibitor". Johnson and Seegers (5) found that incubation of AHG with normal or Type A hemophilic plasma resulted in inactivation of the AHG. AHG, however, could be reactivated by extraction of the incubated mixture with ether, a treatment commonly used for removal of antithrombin III from plasma or serum (6).

The purpose of the study reported herein was to determine whether the hemostatic action of AHG concentrate could be attributable to its capacity of neutralizing antithrombin III.

Materials and Methods

Normal and hemophilic serum. Blood specimens from 100 normal human subjects (including 19 specimens of cord blood) and from 17 Type A hemophilic

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patients, were collected for us in the Department of Hematology at St. Mary's Hospital, Montreal. The clotted specimens were kept at room temperature for six to eight hours and then placed in the refrigerator (5°C) for 24 hours. They were centrifuged, and the serum was removed and stored at 5°C.

Human platelet cofactor (AHG) concentrate. AHG concentrate (Blomback) was produced and provided by Connaught Laboratories of the University of Toronto.

Thrombin standard. Topical Thrombin (1000 N.U./ml), in desiccated form, produced by Parke Davis and Co. The material, dissolved in 1.0 ml of sterile isotonic saline, served as the enzyme preparation.

Fibrinogen preparation. Normal plasma was treated with $BaSO_4$ according to the procedure of Brown et al (7).

Inhibitor preparation. The serum, referred to above, without further treatment, was used as the inhibitor (antithrombin III).

Assay of the thrombin inhibitor. The inhibitor activity of the serum was assayed by a modification of the method of Brown et al. (7) as follows.

To 0.45 ml of serum 0.05 ml of thrombin solution (50 N.U. of thrombin in physiological saline) was added and the preparation incubated at 37°C for 10 minutes. At intervals of 3, 5 and 10 minutes, respectively, 0.1 ml portions were removed and added to 0.2 ml of the fibrinogen preparation. The clotting time of these specimens was determined with the aid of the Adams Thrombitron (Clay Adams, Ltd.).

Percent thrombin activity may be represented as: $A = (1/T)/(1/T_c) \times 100$ where T_c represents the clotting time (in seconds) of the control sample, and T that of the experimental specimen.

The percent or degree of inhibition is: $I = 100\text{-}A$.

Results

Thrombin inhibitor activity of normal and hemophilic sera. Assays were undertaken to compare the inhibitor activity of serum specimens from a number of normal and hemophilic subjects to ascertain the influence of various treatments.

The mean values for the antithrombin activity of normal and hemophilic sera, after various periods of incubation, are indicated in curves A and C, respectively, in Figure 1. The influence of addition of AHG concentrate to the normal and the hemophilic serum is illustrated in curves B and D, respectively. The degree of inhibition (prolongation of the clotting time) was increased with duration of preincubation, and the level of the mean antithrombin activities of both normal and hemophilic sera were lowered on addition of AHG concentrate.

The influence of various additional treatments on the level of the thrombin inhibitor in the sera is indicated in Table I. It is noteworthy that the addition of protamine sulfate to hemophilic serum, or adsorption of the serum with $BaSO_4$, did not decrease the inhibitor activity. A slight decrease occurred on heating normal or hemophilic serum at 56°C for 5 min., and on dialysis against physiological saline at 4°C for 20 hours.

Treatment of hemophilic serum with $BaSO_4$ failed to alter thrombin in-

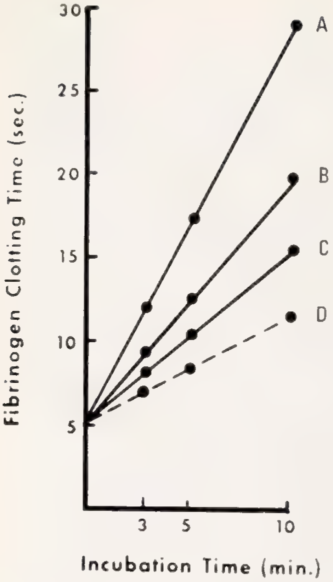

FIG. 1. The influence of AHG concentrate on the antithrombin activity of hemophilic and normal sera. A: hemophilic sera, B: hemophilic sera preincubated at 37°C for 15 minutes with 3.0 mg AHG concentrate per ml. C: normal (control sera), D: normal sera pre-incubated, as in B., with AHG concentrate. Test system: 10 N.U. of thrombin in 0.05 ml physiological saline were added to 0.45 ml serum and incubated at 37°C. At intervals of 2, 5, and 10 minutes, 0.1 ml aliquots were taken and added to 0.2 ml fibrinogen solution. Clotting time was recorded.

hibitory activity, thus indicating absence of residual prothrombin. If prothrombin were present in the serum, it would be activated during incubation in the presence of thrombin and the antithrombin-III level would have been correspondingly reduced.

The addition of thrombin or AHG concentrate to hemophilic serum produced no clot formation. Further, as indicated in Table I, the degree of inhibition of antithrombin-III activity after addition of AHG concentrate was greater with normal than with hemophilic sera.

The concentration of AHG used in these experiments was comparable to that usually administered to arrest bleeding in the hemophilic patient. The AHG solution showed no thrombin activity when added to fibrinogen. The AHG was free of prothrombin because, on addition of 0.1 ml of $CaCl_2$ ($0.025M$), no clot formation occurred even after 6 hours. Furthermore, heating of AHG concentrate to 56°C for 1 hour abolished its capacity to inhibit antithrombin-III.

Discussion

It is evident from Figure 1 and Table I that thrombin inhibitor activity was higher than normal in most hemophiliacs studied. Hemophilic subjects with elevated serum antithrombin have been reported by von Kaulla and von Kaulla (3). Reduction in inhibitor activity was demonstrated in our study on addition of AHG concentrate to both hemophilic and normal sera. It is of interest that the degree of lowering of antithrombin was greater in the normal than in the hemophilic sera.

The question may be raised as to whether increased antithrombin-III activity in hemophilic sera may be attributable to incomplete prothrombin utilization and, in consequence, incomplete formation of autoprothrombin C and thrombin,

TABLE I

Thrombin Inhibitor Activity of Normal and Hemophilic Serum after Various Treatments

Serum Preparation	Inhibition %		
	Mean	Standard error	Number
Normal sera	56.9	0.5	100
Type A hemophilic sera	82.7	0.5	17
Normal sera heated (a)	50.3	0.2	6
Hemophilic sera heated (a)	70.8	0.2	6
Normal sera treated with $BaSO_4$ (b)	56.2	0.3	6
Hemophilic sera treated with $BaSO_4$ (b)	82.7	0.5	8
Normal sera dialysed (c)	48.4	0.3	8
Hemophilic sera dialysed (c)	70.8	0.2	6
Normal sera treated with protamine sulfate (d)	55.8	0.4	6
Hemophilic sera treated with protamine sulfate (d)	82.2	0.4	8
Normal sera + AHG concentrate (e)	37.5	0.2	24
Hemophilic sera + AHG concentrate (e)	66.0	0.4	8
Ether extracted normal sera (f)	none		6
Ether extracted hemophilic sera (f)	none		8

All calculations are based on the values obtained after 50 min incubation of 10 N.U. of thrombin with serum at 37°C.

(a) Heated to 56°C for 3 min. Sample cooled at room temperature and assayed for antithrombin-III activity.
(b) Serum mixed with barium sulfate (0.1 gm/ml) for 15 min in a mechanical mixer; centrifuged at 1,500 × g for 15 min.; supernatant tested for antithrombin activity.
(c) Serum dialyzed against 60 volumes physiologic saline for 20 hours.
(d) Serum mixed with protamine sulfate (3.0 mg/ml) for 15 min. in a mechanical mixer; centrifuged at 1,500 × g for 15 min.; supernatant tested for antithrombin activity.
(e) Serum incubated for 15 min. at 37°C with 3.0 mg AHG concentrate per ml. Antithrombin activity then determined.
(f) Ether extraction carried out according to Seegers et al (6), after which antithrombin activity measured.

and diminished neutralization of antithrombin III. However, clot formation did not follow addition of AHG concentrate and/or thrombin to hemophilic sera. Von Kaulla and von Kaulla (3) observed that antithrombin-III levels in hemophilic sera were independent of thrombin generation. If additional coagulation were to occur in hemophilic sera, the total antithrombin activity in our test system would tend to be increased rather than decreased because fibrin and fibrin fragments have antithrombin activity (antithrombin I and VI).

The addition of protamine sulfate to normal or hemophilic sera, or adsorption of these sera with $BaSO_4$, did not alter levels of thrombin inhibitor. Inhibitor activity of both normal and hemophilic sera was completely abolished on extraction with ether.

We found no evidence of increased proteolytic (tryptic, chymotryptic) or esteratic activity on addition of AHG concentrate to normal or hemophilic sera. The observed lowering of antithrombin activity on addition of AHG concentrate, therefore, could not be attributed to hydrolysis of inhibitor by proteolytic enzymes.

Our findings are consistent with the suggestion of Miles, von Kaulla and von Kaulla (4) that the hemostatic action of AHG concentrate rested with its capacity to neutralize an inhibitor. Since AHG is not yet available in a pure form, one must consider the possibility that some protein other than AHG in the AHG concentrate might be responsible for lowering the level of antithrombin-III.

The observation that serum antithrombin activity frequently is increased in Type A hemophilia and that this activity is diminished on addition of AHG concentrate to either hemophilic or normal whole blood (8), supports the view of an inverse relationship between AHG and antithrombin III, and lends support to Seegers' hypothesis that AHG might function as an "acceptor" of an inhibitor (5). Thus, one may surmise that an increase in the ratio of the concentration of AHG to antithrombin III could favor clot formation while a decrease could tend to retard coagulation.

A study on the kinetics of the thrombin-fibrinogen-inhibitor and the thrombin-fibrinogen-inhibitor-AHG systems is reported in another paper.

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Aging*

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The author of this paper on aging is herself in the ninth decade. A psychiatrist in active practice, Dr. Knopf is vital, vigorous, and alert. Her views of the problem, as seen from within, are of interest. (*Editor's note*)

What is aging? Aging, like growing up and maturing, is a process which does not occur at the same rate in every individual, in the same sequence, nor with the same intensity. The onset is gradual under normal conditions, and is more dramatic under stress. Aging results in a decline in functional capacity, lessened resilience, and increased vulnerability of the organism to stress and to disease; everyone of these manifestations is progressive and irreversible. Stress may occur from within, from a physical condition, or an emotional or intellectual experience; the impact need not be a major one. A common cold, for instance, may precipitate stress. The most important stress, however, is, in my opinion, the reaction of the individual himself to his aging. The manifestations of aging must be differentiated from chronic illness although they usually occur during the same age period of life and have a strong interaction with each other. Stresses from without are caused by changes in the environment, the social and economic conditions due to retirement, and, last but not least, the relationship of the individual with his family and friends.

All this is very well known. Many good books have been written on this topic, and, if the above were all there is this paper would not need to be written. But what it feels like to *be* old is not known because nobody wants to know, not even the old ones themselves.

The reasons for the disinclination of younger people to deal with the aged are manifold. In dealing with the aged, younger people have to come to grips with their own unresolved or incompletely resolved Oedipus situations, with their own concept of aging, and their attitude towards pain, illness, and death (1).

The most important reason, however, is the inability of any individual to project himself into the future. As a preceptor, I have had ample opportunity to observe residents in their contact with aged patients, and I found them often to be at a disadvantage. They and any other younger person cannot imagine what an old person feels, and the aged patient cannot explain because most of them hide their true feelings or are unable to verbalize them. The younger physician, in turn, is not relaxed in his approach to the patient; he has inhibitions against "intrusion into an old person's privacy." It is as if he were to ask intimate questions of a parent.

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The inability to project oneself into the future is easily explained—empathy, the most important skill of any psychiatrist, is based on the ability to put oneself in the patient's place. We remember similar situations or conflicts from our own past, from our own childhood and later periods of life, and compare these with the patient's actions and feelings, while we remain aware of the fact that we are not the patient. No such projection is possible for life situations that lie ahead of us. Nobody can visualize what he will be like 20 or 30 years hence.

This statement can be tested any time when we observe how unrealistically people conceive of their own future. Ask anyone what he will do after retiring. The answers one gets most often show clearly that whatever plans are made, they are made with the present state of health and vigor in mind and do not take any decline into consideration. Moreover, the plans for the future contain in many instances pipedreams which are not ever to be realized. When the time comes in which these fantasies and plans can actually be put into practice, the great disillusionment sets in with all the consequences which may lead to an emotional crisis.

How can the bridge be made between a reluctant patient and a self-conscious physician? If what is happening in the aging process is actually spelled out, at least in part, the ingenuity of the psychiatrist can be of great help in explaining these happenings to the aged patient. The obligation to try to reach the patients lies with the therapist, and an educated guess sometimes breaks the ice and convinces the patient that a younger person does understand what an old person feels and fears.

Let us look first at the changes coming from within the body and let us begin with the five senses. Impairment of sight and hearing is generally accepted as a sign of getting old. Touch, taste, and smell are equally affected but their changes are not sufficiently appreciated. Discontent with food is the most frequent complaint in any old people's home. Taste buds become duller; they are being replaced every few days but in later life replacement is slower, hence, impaired taste. Dentures, too, diminish the savoring of food because they cover a large portion of the oral cavity. The recently discovered illness, idiopathic hypogeusia, attacks taste and smell and occurs mainly among older people (2).

The sense of touch and the position sense lose a great deal of sensitivity as times goes on. Older people drop things oftener than they used to. In addition to the diminished sense of touch, the muscle sense and muscle strength changes too. This applies equally to the voluntary and involuntary muscle groups. The same effort that lifted a foot for safe walking is not sufficient in later years. The result is more frequent stumbling, falling, and fractures. More exertion is needed to take a firm grip when carrying or handling objects. Digestion and elimination are affected too and are sometimes a source of embarrassment to a fastidious oldster.

Staying power diminishes as well, and so does the tempo with which daily chores can be accomplished compared to the past. More time is needed for the same activities; the schedule lags and at the end of the day the older person feels harrassed and driven without having accomplished what he had set out to do. The result is frustration and anger at oneself.

Memory slows down and so does the ability for new learning. The emotions become flatter, wherein lies the real source of the time-honored myth about the aged becoming more mellow and more tolerant. In truth, they simply care less.

The sexual drive undergoes the same slowing-down process. There are, however, great individual differences depending on the general state of health, the setting in which the old person lives and his gender (3). Married couples continue or discontinue their sexual activities more or less by mutual agreement proportionate to their human relationship. The better they get along as people, the less change in their sexual understanding is to be expected with the exception of decreased frequency.

If the marriage has broken up either by divorce or the death of one mate, the gender decides what may happen in later years. While the sexual appetite remains pretty much alive for both men and women, the opportunity for expressing it differs sharply as time goes on. The male has almost no limitations in expressing and gratifying his sexual desires as long as his physical condition remains good. History and biography inform us of the sexual prowess of men in their eighties. Female sexual attractiveness diminishes around fifty and to a larger degree than that of the male. Moreover, the mistaken concept that the menopause puts an end to a woman's sexual desire and needs has its psychological effect both on women and men. Actually the menopause puts an end to a woman's fertility but changes nothing in her ability to desire and to enjoy sexual activity for many years to come. When this point came up in a discussion during a group therapy session with some old men and women, a woman around 70 stated: "A woman would like to have sex, too, but she does not have the opportunity."

Self-respect suffers blow after blow. Self-reproach for falling down on the job and subsequent self-hatred is followed by guilt feeling. The list of frustrations, pain and disappointments can be expanded almost indefinitely. One factor especially is not to be underestimated, at least not as far as women are concerned, and that is appearance. Looking at oneself in the mirror is a daily shock from which there is no escape. To make a long story short—the self-esteem of the aged person is beset from every angle. The ego-ideal becomes more and more unattainable, guilt feelings grow, and so does depression. This can be seen from the usual complaints about bad sleep. I remember an old man who still functioned very well in every day life who said: "At night I think of all the things I should have done and didn't do."

To all these impacts an old person must cope with, the many chronic diseases that plague him in the course of time must be added. Some of them cause a great deal of pain and, therefore, diminish the zest for living, even if they do not represent a threat to life. Others restrict mobility and force the individual into further withdrawal.

It is my belief that there is not a single aged individual who is not depressed, at least part of the time. Anger is directed more against the self than against anyone in the outside world, as has been pointed out by Robert H. Dovenmuhle (4). This self-hatred and self-rejection explain at least in part the increased rate of suicide among the very old. They also explain the various defenses an aged person will establish like hypochondriasis, dependency, and increased demands on family and friends. Here is where the family doctor or the psychiatrist can be most helpful to the patient. First he must take care of the physical condition of his patient and make him or her as comfortable as possible. He can do more: he can explain what happens during aging. He can acquaint the patient with himself and enlist the patient's assistance in combatting as many of the drawbacks as possible. For instance, he can encourage the patient to lift the foot higher when walking, to grip objects more firmly and with both hands where once one hand would have done, to give himself more time to do the daily chores, and not to be embarrassed to take frequent rests. A momentary lapse of memory is often the cause of embarrassment of an aged person. It occurs mostly in social situations like the remembering of a name. The advice to the aged is to accept this lapse instead of fretting over it.

In short, what the doctor or the psychiatrist can try to accomplish with his patient is to turn the self-hatred into self-acceptance. This is by no means to be confused with self-indulgence. The accent lies here on integrating the new knowledge of oneself into one's daily life. The removal of guilt feelings in consequence can set a great amount of psychic energy free, which then can be applied to more satisfactory purposes.

The collective term for the changes that are forced upon the aged by the environment is a rather glib one—socioeconomic. It is a technical term that hides the real meaning more than describes it. Most of its elements can be better taken care of by social service than by psychiatry; but these stresses deserve to be enumerated because some of them are of considerable influence on the patient. They concern loss of mate, close relatives, and friends through death, retirement, not always voluntarily, and subsequent reduction of income, forced retrenchment of standard of living, dislocation, loss of prestige in the community, economic dependence on children or family, and, added to all these, impairment of health precipitated by these stresses.

All these privations coincide with the physical aging process and with the occurrence or aggravation of chronic diseases. The solution to these problems brings us to the next task the psychiatrist has to shoulder, namely, assisting the patient in reorganizing his life after discharge from treatment. Here we have to take the lead from the patient and the kind of life he lived before. On the whole, there are two main groups to be considered: the self-employed and people who work for others.

The self-employed are not subject to the fateful year 65. They usually continue to work beyond that time and retire when they take sick and feel worn out and then they are glad to get a rest. They usually retire when much older than 65. The homemaker will also continue her activities so long as her husband works or is alive. Her critical time comes either with his final retirement or his death. Having the husband home for lunch may upset the life she as been used to. Her compatibility with her husband is now exposed to a crucial test. Some couples now find out they share very few fields of interest. When the husband dies the new adjustment for the wife is closely connected with her relationship with her children and with the economic level of her existence.

In cases in which the old one must retire at 65, the situation is more complicated. Some are still too vigorous just to sit, while others cannot wait until they can sit. The latter come usually from the ranks of people whose jobs demanded a great deal of physical exertion.

Time weighs heavily on the retired person and the lack of a daily routine hits some people very hard. Much as a hard-working person dreams about leisure, once it becomes daily, fare boredom results and leisure becomes a burden. Diversions are sought, but their lures do not last long. An aged person is very lucky if he has a hobby which he now can pursue with greater intensity. The broader the educational basis the more room there is for new and absorbing interests. Others follow a sideline of their former activity, thus staying closer to home and yet accepting a new challenge.

Still others, and this is the majority—depend on stimulation coming from outside to escape loneliness. They join Golden Age clubs in their neighborhood or move to communities established for the aged. This new trend of founding special housing projects and even special communities for the aged is, to put it mildly, a mixed blessing. The one advantage of the ensuing publicity is the acknowledgment that old people need attention and more consideration than they have received in the recent past.

Since the advent of the machine age the aged have been more and more pushed aside. The flight from the farm and from smaller communities into the large cities created a shortage of living space for the aged. The dispersion of families left the aged to shift for themselves in their later years. It is a step forward to try to collect them from their hall-bedrooms and rooming houses and provide companionship they so badly need. The communes for the aged furnish companionship and health care for people who can afford it and the Golden Age clubs do the same in cities for people with more limited means. The fact that there are 160 such clubs in Manhattan alone describes the need better than words (5).

The old people themselves would prefer to have the familiar companionship of a mate, friends, or family; in short, they like to associate with people who can share their memories of days gone by or with whom they have more closely-knit ties than with casual club members or social workers. Missed in these communities almost more than anything else are the laughter and caresses small children bestow so liberally on their grandparents. During a group therapy session in one of the Golden Age clubs the old ones requested parties where they could entertain small children. This was what they missed most in their present mode of living. To quote Dr. Norman E. Zinberg, ". . . a community without older people is almost as sterile as one without children" (1).

I am not sure that it is only the economic pressure of their middle-aged children that forces the old ones to shift for themselves in such large numbers.

Something else has gone amiss in the relationship between the middle-aged and their aged parents. It is readily conceded that there are a great many families who venerate their aged members and who take care of them not only financially but who also satisfy their emotional needs. It is also conceded that there are a great many aged men and women who are unreasonable in their demands on their middle-aged children who, themselves, may not be in good health or who have many worries with their own offspring.

Yet, on the whole, it seems that the tension between these two generations is just as great as the generation gap between younger parents and their teenage children. The old ones are too embarrassed to talk about their differences with their children and grandchildren, and they persuade themselves that it is only they who have problems with the family, while other families live in eternal bliss with one another.

In listening to the complaints of the aged, one can learn how disappointed they are in the attention and care they receive from their children. No matter how strongly the old one professes to desire independence, he or she wants and needs the proximity and protection of the younger generation. The parents feel they have earned it by the care they gave their children when they were small, that they have earned some sacrifices on the part of the children through their self-denials that were necessary to give the children their chance in life. Yet, these children very often feel that the expectations of the parent are unreasonable. There is an old saying that one parent can bring up six children, while six children cannot take care of one parent. Where there is discontent, we will find more often than not that the charges of the old one are not unjustified. On the other hand, the children have their side, too, and it is here that the psychiatrist can be very helpful. One of the earliest publications by Freud, "Three Essays on the Theory of Sexuality," investigates the psychodynamics of these conflicting attitudes (6). Freud speaks of the active repetition of a passive experience. Through this mechanism, the child gains mastery over a trauma. Consider a child's first trip to the dentist's office, after which he will repair the teeth of the younger siblings and everyone else's he can lay his hands on.

Applied to the child-parent relationship, we see that the child, as adult, repeats actively in his behavior toward his own children whatever he received passively from his parents. Thus, he does not feel that he owes something to his aged parent, while the old parent expects some return for his early sacrifices. Obligations in later life are earned more or less on an adult level, and these are frequently rather precarious. All this can be explained to the patient and to the children and can be helpful in the therapeutic process.

The relationship of the child at any age to his parents is a very complicated and intricate affair. I shall pick out only two elements that are pertinent in the present discussion. One is that the child has emotional difficulties seeing his parent's decline in later years. The small child derives his strength from the strength and support he receives from the parent, and some of these manifestations never quite disappear. To see the strength of the parent diminish represents a threat to the child, no matter of what age. The parent's decline reactivates old conflicts and ambivalences. The reaction of the child may lead either to over-solicitude or rejection of the parents. Both are detrimental to the aged one. Over-solicitude infantilizes; rejection hurts even more.

The other element to be mentioned is the fact that the child rather often conceives of himself in relation to the parent as being on the receiving end forever. Just as he expected, when small, to be supported and assisted by the parent at all times as his due, he never quite loses this expectation. Not being able to project himself into the future, he sometimes also cannot understand that an older person has a right to live, a right to get help from the younger ones. In the eyes of the children it is sometimes as if the parent, by living as long as he does, were taking something away from what belonged to the children. Social Security has ameliorated this situation, but only to a very small extent. The cruelty of some children arises from their inability to put themselves in their parents' shoes.

What can psychiatry do? In the last analysis, psychotherapy is an educational process. We acquaint the patient with his psychic mechanisms, his motivations and aims. By giving the patient insight, we teach him to utilize his potentialities to better advantage. We can also teach him to make concessions where necessary and to accept situations that cannot be changed. The process of living is a series of adaptations and compromises at all times, but most adaptations are demanded at an age when man is least flexible in complying.

However, the picture I have drawn is actually less dismal than it sounds. First, the changes occur gradually, over a long period of time. They do not all occur at the same time and some need not happen at all. Once an old person learns to accept himself and his limitations, he may also learn that getting old has a number of advantages. The removal of the pressure of work, of responsibility, and of having to keep a time schedule are advantages not to be underestimated. With some initiative one can create new fields of activities and interests simply by dropping the competitive component of one's former calling. The old one can take pride in things he can still do and need not cry over the things he can no longer do.

In discussing an old person's attitude towards death, we must distinguish between the aged up to 75 years, and those over 75. As long as old people are active and physically fairly well, there is very little concern about dying. It is during times of illness that actual fear of dying and hypochondriacal tendencies occur, although the fear of dying is ostensibly related to the illness itself. The over-aged are more aware of death even when living normal lives; but death is a topic that is not discussed among them. Preoccupation with death appears only in the avoidance of long-term planning and in remarks to an enterprising contemporary like, "It is later than you think." The ever dwindling number of friends or family members is saddening, but I am convinced that the survivor's attitude is best compared to that of the soldier in the field who hopes that the oncoming bullet does not have his number on it. The deciding factor seems to be the state of health.

When feeling fairly comfortable, old people enjoy living as much as the young ones, especially when involved in some undertaking that holds their interest. Also, when they have the feeling of being needed and still being able to hold their own, there is no thought of not living or not wanting to live.

If, however, life becomes painful, physically or emotionally, death is frequently thought of as a way out. I know that some of my contemporaries have accumulated a lethal dose of sedatives, as a reassurance that they can terminate their suffering, just in case. What they would actually do in a crisis is hard to say. On the whole, I believe that death holds no threat to they very old if it comes without suffering. Everyone of us has moments in which he realizes that his time is limited. The one thing to do is to utilize what is left as well as possible.

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Systemic Mastocytosis and Multiple Carcinomas

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Abstract

The clinical and pathologic features of a case of long-standing systemic mastocytosis are presented. Although fibrosis and enlargement of the liver, spleen and lymph nodes, and specific abnormalities in the bones were all consistent with mastocytosis, a paucity of mast cells were identified in these organs at postmortem examination. Terminal infections included widespread cytomegalic inclusion disease. Three distinct carcinomas, one detected and treated during life and two discovered at autopsy, were associated findings. Lympho- and myeloproliferative malignancies in mast cell disease have been documented, but a relationship between systemic mastocytosis and the development of eipthelial malignancies has not been previously reported.

Introduction

Systemic mastocytosis is an uncommon reticuloendothelial disorder characterized by tissue mast cell invasion of skin, bones, and internal organs. The specific granules of the mast cells have been shown to contain histamine (1) which may in part account for many of the physiologic findings of pruritis, flushing, tachycardia, and duodenal ulceration (2). The release of heparin, also contained within the granules (3), may explain the occasional report of an abnormal bleeding time in patients with mastocytosis (4). Mast cell disease has an extremely variable clinical course and rarely is found in association with a myeloproliferative or lymphoproliferative malignancy (5–10). This may reflect a variant of undifferentiated growth from the original reticuloendothelial cell. Carcinomatous neoplasms to date have not been reported in patients with systemic mast cell disease. We have studied and herein report a patient with mastocytosis who had multiple epithelial malignancies.

Case Report

R. G. (MSH #737859), a 65-year-old retired insurance executive, had developed a generalized, erythematous, papular skin eruption over the trunk and extremities when he was in his "late twenties". A biopsy of one of these lesions indicated the presence of mast cells. Over the ensuing twenty years, the patient developed insidious enlargement of the liver and spleen in association with radiographic evidence of widening of the medullary bone cavities and patchy areas of sclerosis. On this basis, a diagnosis of urticaria pigmentosa with transition to systemic mast cell disease was established. He was able to live a normal life and was only incapacitated by gouty arthritis, well controlled on a regimen of benemid, colchicine, and moderate dietary restriction. Intermittent pruritis was not exacerbated by solar exposure and was controlled by antihistamines.

In April 1968, the patient reported right ear pain and decreased hearing. An adenocystic carcinoma (Fig. 1) was identified involving the right maxillary, ethmoid and sphenoid sinuses, and hard and soft palate. He received a total of 5900 rads to the area during a two-

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month period of time which produced a conspicuous diminution of pain and a decrease in the size of the tumor mass.

In October 1968, the patient was admitted to The Mount Sinai Hospital with extreme weakness. The skin of the trunk and extremities was covered by a maculopapular eruption which was both erythematous and brown. Dermatographia was demonstrated. There was a well-healed biopsy scar on the posterior right palate which was surrounded by postirradiation mucosal changes. A firm liver edge was felt 5 cm below the right costal margin and a firm edge of the spleen was identified 13 cm below the left costal margin. There was no peripheral lymphadenopathy.

Laboratory studies were as follows: Hgb 9.5 gm%, Hct 29%, Wbc 29,000 cells/mm^3 with a differential consisting of 1% band forms, 29% PMN, 51% eosinophils, 1% basophils, 14% lymphocytes and 4% monocytes; the platelet count was 94,000 cells/mm^3 and the number of reticulocytes 1.5%. Sternal bone marrow aspiration yielded normal cellular material with a normal number of megakaryocytes, but approximately 50% of cells were eosinophilic myelocytes and there was a slight increase in mast cells. The bleeding time was prolonged to 14 minutes (normal < 5 minutes), but prothrombin time, partial thromboplastin time, and fibrinogen level were within normal limits. Uric acid was 10.1 mg%. Chest X-ray demonstrated patchy osteoporosis of the ribs but no abnormality of the heart or lungs. A bone survey disclosed generalized osteoporosis with widening of medullary cavities and coarsening of trabecular patterns. Patchy sclerosis was present throughout all the bones, particularly in the calvarium.

Radiographic examination of the colon was normal except for a questionable area of narrowing in the sigmoid region. An upper gastrointestinal series showed a small hiatus hernia and a deformed duodenal bulb. Despite a normal small bowel by x-ray examination, there was definite chemical evidence of malabsorption. Serum cholesterol was 98 mg%; fasting serum carotene was low; vitamin A tolerance curve was flat, and d-xylose absorption

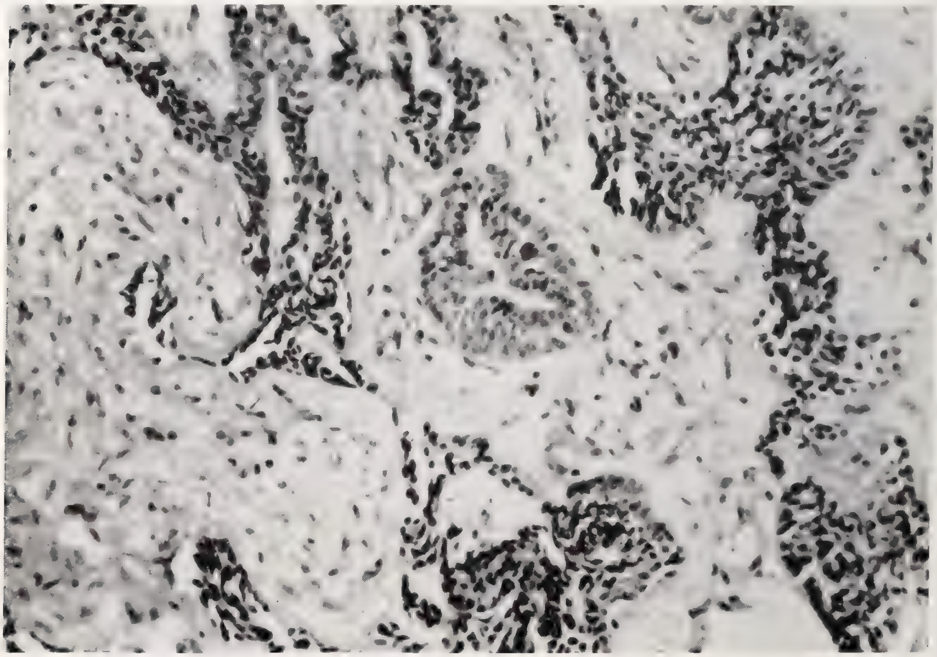

FIG. 1. Adenocystic carcinoma of the soft palate. (Hematoxylin and eosin × 100)

was abnormal. Serum folic acid was 1.6 mμg/ml (normal 7–15) and serum vitamin B_{12} was 2,100 μμg/ml (normal (200–800). Blood histamine and serotonin and urinary levels of 5-hydroxyindole acetic acid were not elevated.

The symptoms of pruritis were controlled by cyproheptadine. In an attempt to reduce the huge spleen and influence the malabsorption, oral cyclophosphamide, in a dose of 100 to 200 mgs per day was given. On this medication, spleen size diminished by about 50% and the white blood cells decreased to 10,000 per mm^3, but the patient continued to lose weight and deteriorate slowly. The patient had taken prednisone, 10 mg per day, as an antibasophil agent for over three years preceding admission, and this medication was continued in the hospital. One month prior to death, massive duodenal bleeding was controlled by a vigorous antacid regimen. Despite a high caloric diet and physical therapy, the patient became more debilitated and died in January, 1969, approximately 35 years after the onset of mast cell disease. The terminal illness was pneumococcal bronchopneumonia.

At postmortem examination, widespread macular and papular lesions were noted on the scalp, extremities, and trunk. Multiple sections of skin showed numerous mast cells and some esosinophils infiltrating the upper dermis. Two small peptic ulcers were present in the duodenum. A mucin producing adenocarcinoma was observed in the sigmoid colon with metastases to regional lymph nodes (Fig. 2). An enlarged liver (3100 gm) contained approximately six well-circumscribed, firm, white, 3 cm in diameter tumor masses scattered throughout both lobes. All showed transition from normal bile duct structures to a distinct adenocarcinoma pattern of the bile ductular type (Fig. 3). Special stains failed to demonstrate the presence of mucin in these multiple tumors. A moderate degree of portal fibrosis and some nonspecific inflammatory cells in the portal tracts were noted in the remainder of the liver. Metachromatic stains did not reveal mast cells. The spleen weighed 1,500 grams and had prominent fibrosis, moderate reticuloendothelial hyperplasia, and depleted lymph fol-

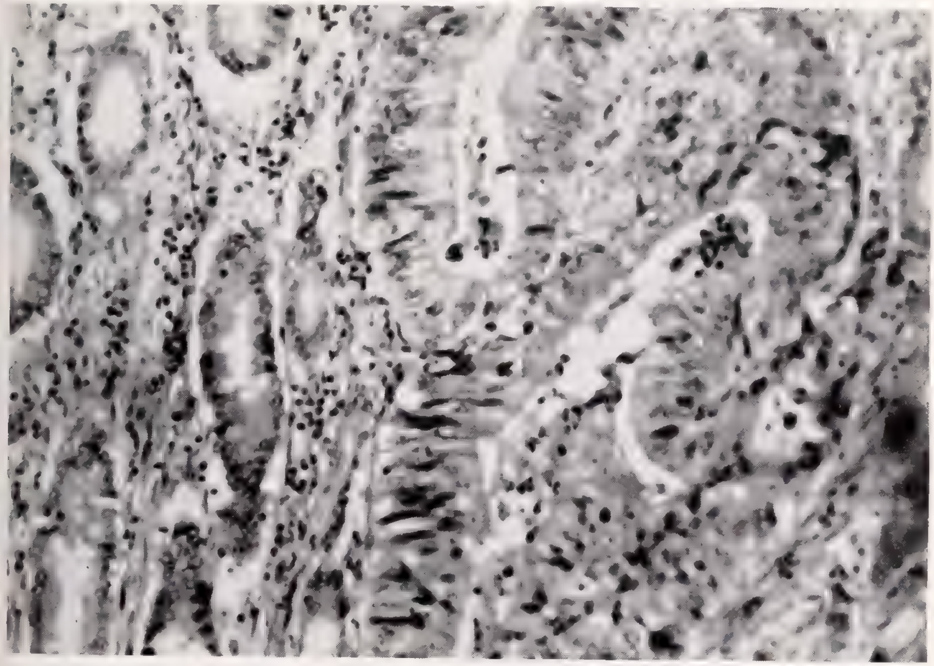

FIG. 2. Mucin-producing adenocarcinoma of the sigmoid colon. (Hematoxylin and eosin × 100)

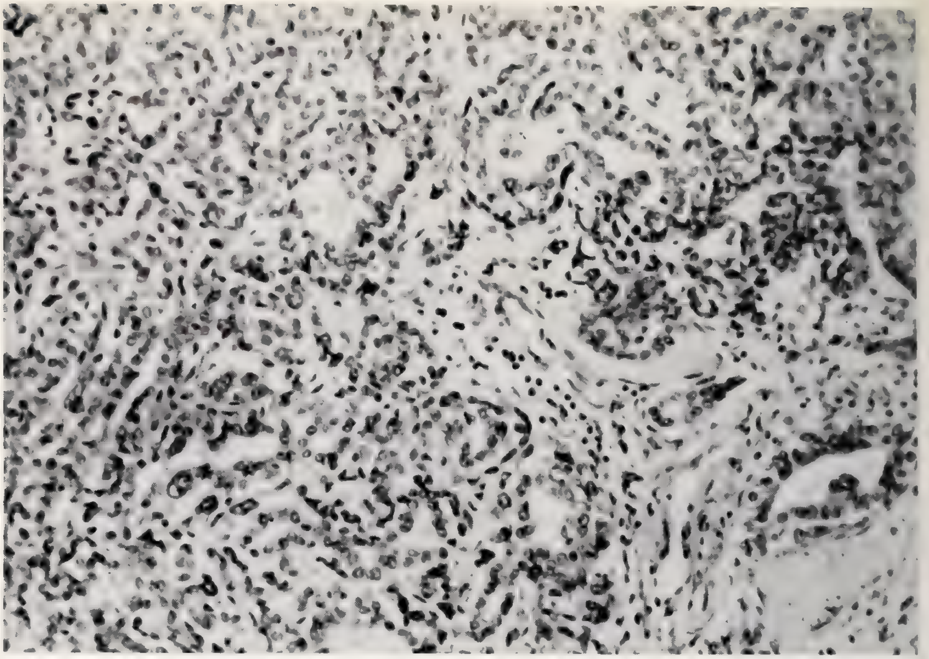

FIG. 3. Cholangiocarcinoma of the liver surrounding a portal tract. (Hematoxylin and eosin × 100)

licles. Mast cells in any sizable number were not demonstrated, but eosinophils were diffusely scattered throughout. Prominent were numerous large macrophages with eosinophilic cytoplasm and large nuclei containing cytomegalic inclusion bodies. Mediastinal and abdominal lymph nodes were all diffusely enlarged and contained an increased number of eosinophils, but no mast cells. Vertebral and sternal bone was abnormal, showing marked osteosclerosis and new bone formation alternating with regions of thinner trabaculae and focal fibrosis. Numerous eosinophils and small numbers of mast cells were present. A 2.5 cm firm, white, well-demarcated mass protruded from the capsular surface of the upper pole of the right kidney. On microscopic examination, this was a papillary adenoma. An extensive necrotizing bronchopneumonia occupied the entire left lower lobe of the lung.

Comment

Fibrosis in systemic mast cell disease, as noted in our patient, is well documented (2, 11, 12). Although the precise mechanism for the increased fibrosis is unknown, it may be related to the ability of heparin to enhance the formation of collagen from its soluble forms (13). The absence of large numbers of mast cells and the presence of eosinophils in reticuloendothelial organs in our patient at the time of death is not inconsistent with the diagnosis of mastocytosis and may be explained in several ways.

Shortly before death he received cyclophosphamide in combination in adrenocorticosteroids which reduced white blood cells from 30,000 to 10,000 per mm^3 and decreased the size of the spleen by 50 percent. Both agents have been reported to produce disruption and regression of mast cell lesions (14 and 15). Severe infection alone, which preceded death, was considered to be the cause of mast cell depletion by Holti (16). Our patient expired with extensive bronchopneumonia and widespread cytomegalic inclusion disease, which in an analogous fashion might have contributed to the disappearance of the mast cells. The numerous eosinophils throughout the organs support rather than negate the diagnosis of systemic mast cell disease. Infiltration of the liver, spleen and bone marrow, among other sites, has been observed many times (2, 5, 17). The exact relationship between mast cells and eosinophils is not clear, but one can speculate that eosinophils serve to detoxify histamine liberated by the mast cell (18). Thus, the autopsy findings in our patient are compatible with long-standing mast cell disease modified by cytotoxic and steroid treatment and complicated by a terminal infection.

The mast and other cells of the hematopoietic system are derived from an undifferentiated mesenchymal cell through an "activated" reticulum cell (19). It is not surprising, therefore, that a number of papers have described the systemic form of the disease occurring with lympho- and myeloproliferative malignancies exclusive of mast cell leukemia. Balbi (7) reported an eight-year-old child with a life-long history of mast cell disease dying with acute hematocytoblastic leukemia. A patient of Sagher et al (5) died with myeloid leukemia and fibrosis of the liver and spleen fifteen years after the onset of mastocytosis. Sagher et al (6) described another patient in whom monocytic leukemia developed five years after the diagnosis of urticaria pigmentosa. Autopsy revealed both leukemic and mast cell infiltration of the internal viscera. Bowdler and Tullett (8) reported a patient with polycythemia vera following a one-year history of urticaria pigmentosa and mast cell infiltration of the bone marrow. A patient of Weidman and Franks (9) was a 52-year-old man with an 11-year history of urticaria pigmentosa who developed adenopathy. Lymph node biopsy showed both Hodgkin's disease and numerous mast cells. Nixon (10) described a patient in whom a diagnosis of lymphosarcoma was made 15 years after the onset of mast cell disease. On postmortem examination, there was extensive lymphosarcoma in many organs; mast cells were absent and the author thought that the primary cell had converted to the production of lymphocytes, rather than mast cells.

By contrast, an epithelial malignant tumor has been reported in association with urticaria pigmentosa, but to our knowledge has not been noted in patients with systemic mast cell disease. In this case discussed by Cohen et al (20), urticaria pigmentosa disappeared after resection of a colonic adenocarcinoma and did not recur when the tumor disseminated at a later date, and thus might have been a reaction to the presence of the primary tumor. It appears that our patient is the first in whom systemic mastocytosis and carcinoma, in particular multiple tumors, have been observed together. Warren and Gates (21) require cytologic evidence of malignancy, a distinct histologic pattern, and a separate confined area of spread in order to establish a diagnosis of multiple primary malignant neoplasms. Our patient had three distinct carcinomas: adenocystic carcinoma of the nasopharynx, multicentric cholangio-carcinoma of the liver, and adenocarcinoma of the sigmoid colon. These tumors satisfy the criteria of these authors.

Acknowledgment

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Obstruction of the Small Intestine Caused by Endometriosis

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Small bowel obstruction caused by endometriosis is not commonly encountered, yet a review of the literature indicates reports of several cases each year for the past 5 years. The diagnosis is rarely made preoperatively and, unless the surgeon is cognizant of this entity, the specific diagnosis may not be appreciated until the microscopic study of the specimen is completed. The following case is illustrative of many typical features of small intestinal endometriosis with intestinal obstruction.

Case Report

J.B. NO. E5795-71. A 28-year-old Filipino woman was seen in the clinic of Elmhurst Hospital on September 15, 1971 complaining of intermittent nausea, vomiting, epigastric pain, and diarrhea for three days. Her history was not remarkable except for premenstrual migraine headaches and lower abdominal cramps which had become progressively worse over the past seven years. She had no previous surgical operations.

The physical examination was entirely normal; her temperature was normal. She was treated symptomatically with Lomotil® and Donnatal®. Her symptoms subsided somewhat but recurred ten days later just prior to her menstrual period; at this time she also had her usual premenstrual lower abdominal cramps. The physical examination was unchanged except for some periumbilical tenderness. A suspected gastroenteritis was treated with Maalox®, Probanthine®, and Compazine®.

On October 1, 1971, the crampy abdominal pain and periodic vomiting returned and became progressively worse for the next three days. After vomiting all food and fluids for 24 hours, she was admitted as an inpatient October 5, 1971. She had a few scanty watery stools in the previous two days. Recurrent periumbilical and epigastric pains were severe. Examination revealed a moderately dehydrated petite female in acute distress. The abdomen was distended and exhibited tenderness primarily focused around the umbilicus and epigastrium but also elicited on palpation of the upper and lower quadrants of the right abdomen. No abnormal abdominal masses were palpable. Bowel sounds were absent except for an occasional tinkle. Rectal and pelvic examinations were not remarkable.

Her temperature was 100.4 degrees. The pulse, blood pressure, and respiration were within normal limits. The urine examination disclosed a strong acetonuria. Blood examination revealed the following: Hemoglobin, 15 grams; hematocrit, 45; white blood cell count, 7100 with a marked left shift; serum sodium, potassium, and chloride were mildly below normal.

The diagnosis was obscure and many possibilities were considered, including ileus secondary to a sealed-off perforation of a viscus or foreign body, strangulated appendix epiploicus or omentum, intussusception, pancreatitis, internal hernia, and gastroenteritis. An intestinal tube was passed and intravenous fluids with electrolytes were administered. The intestinal tube drained a murky material with fecal odor. Abdominal x-rays were taken and demonstrated dilated small bowel loops with fluid levels as seen in intestinal obstruction (Fig. 1). After 20 hours of further observation, the temperature rose to 101 degrees, no clinical improvement was noted, and a laparotomy was performed through a right paramedian incision. The small bowel was dilated down to the point of obstruction four and one-half inches from the ileocecal junction. The distal ileum was collapsed. The segment of ileum, approximately two inches long, at the point of obstruction was involved in a cicatricial process exhibiting multi-

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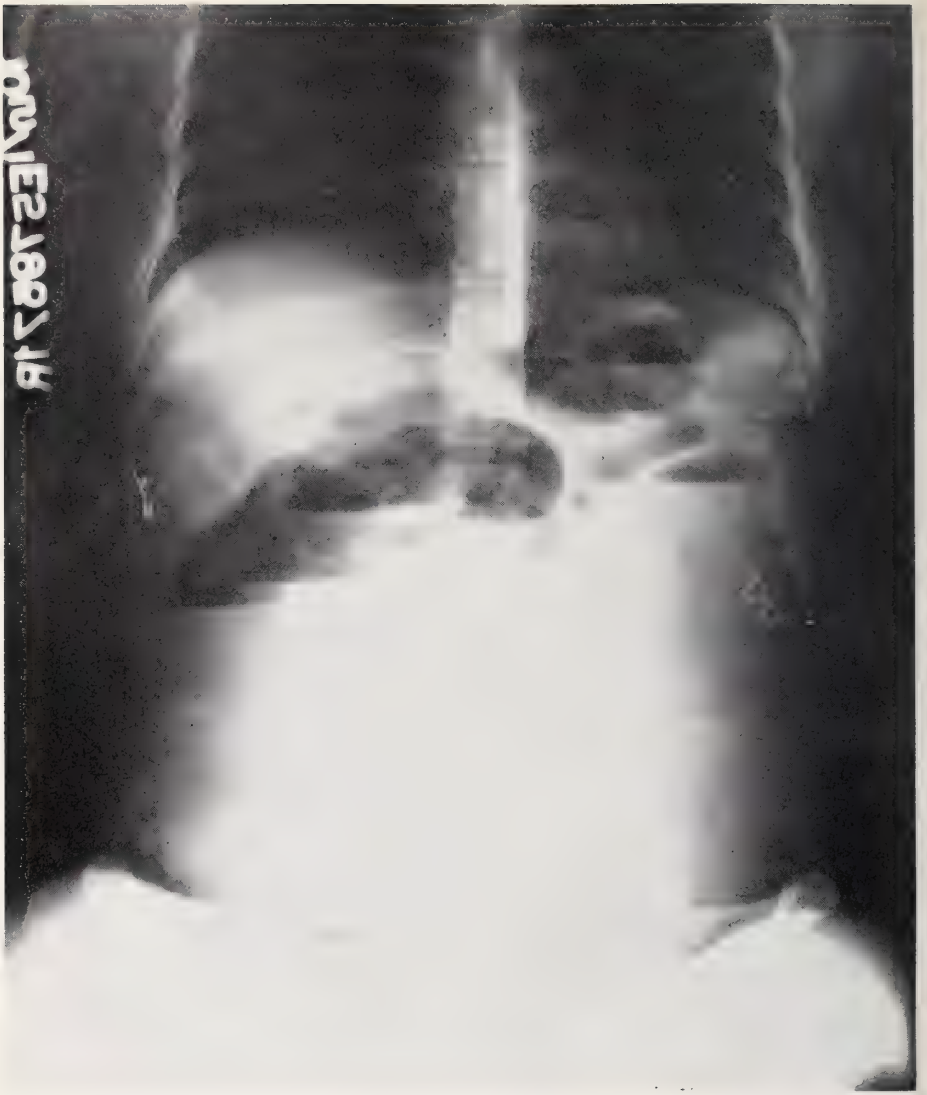

Fig. 1. Upright roentgenogram of the abdomen. Multiple dilated loops of small bowel with fluid levels are indicative of ileal obstruction.

ple longitudinal thickenings which appeared to invaginate the serosa of the bowel. This area was also adherent to a segment of omentum. The operative impression was that the adhesive bands were probably congenital. The involved area was resected and intestinal continuity was restored by an end-to-end anastomosis.

The pathological specimen revealed a constriction of the bowel in which the mucosa was pink and moderately edematous but showed no circumscribed lesion. The serosal aspect exhibited a white fibrous constricting band 1 cm in length and 0.5 cm in width. Focal areas of hemorrhage were also seen on the serosal aspect (Fig. 2). The omentum was spotted with focal thickened areas of red or brown color and a few tiny cystic areas. Microscopic

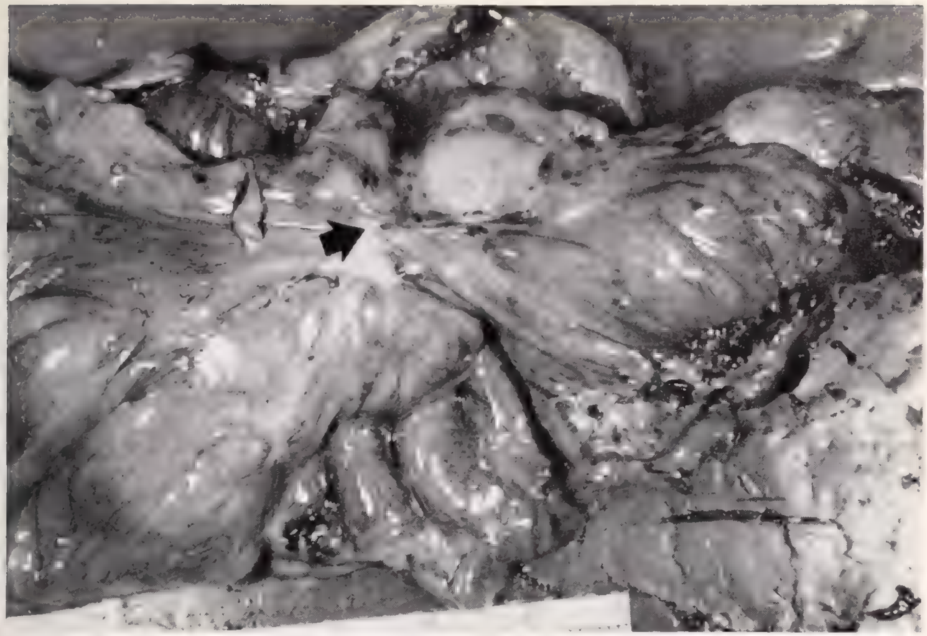

FIG. 2. Segment of ileum removed shows dense fibrosis and serosal puckering (arrow) with adjacent focal hemorrhagic areas of endometriosis.

examination of the small bowel showed multiple foci of endometrial stroma and glands lined by columnar cells in the serosa and in some places extending into the outer muscular coat. The serosa in these areas was thickened by dense fibrous tissue proliferations. Sections of the mesentery and omentum also showed foci of endometrial tissue (Fig. 3).

The patient had a satisfactory postoperative course with the exception of a small wound abscess from which E. aerogenes was cultured; this was the same organism cultured from the peritoneal fluid at the time of the operation. The wound was almost completely healed when she left the hospital 12 days after surgery. Her postoperative menstrual periods have not been accompanied by any pain for the first time in seven years.

Discussion

Endometriosis is a common lesion of uncertain pathogenesis which continues to present problems in diagnosis and treatment. The theories of pathogenesis vary in their ability to account for the presence of endometrial tissue in such widely scattered areas as lymph nodes, pleura, lungs, hernial sacs, wound scars, umbilicus, and gastrointestinal tract. It is probable that more than one mechanism plays a role. The most plausible theory which can account for the intraabdominal dissemination is a transtubal reflux with peritoneal implantation. Lymphatic embolization may account for the lymph node lesions. Experimental lesions have been produced by injection of endometrial tissue into veins. The theory of coelomic metaplasia also may possibly account for most instances of endometriosis (1).

A review of 7,177 cases of endometriosis has disclosed an incidence of in-

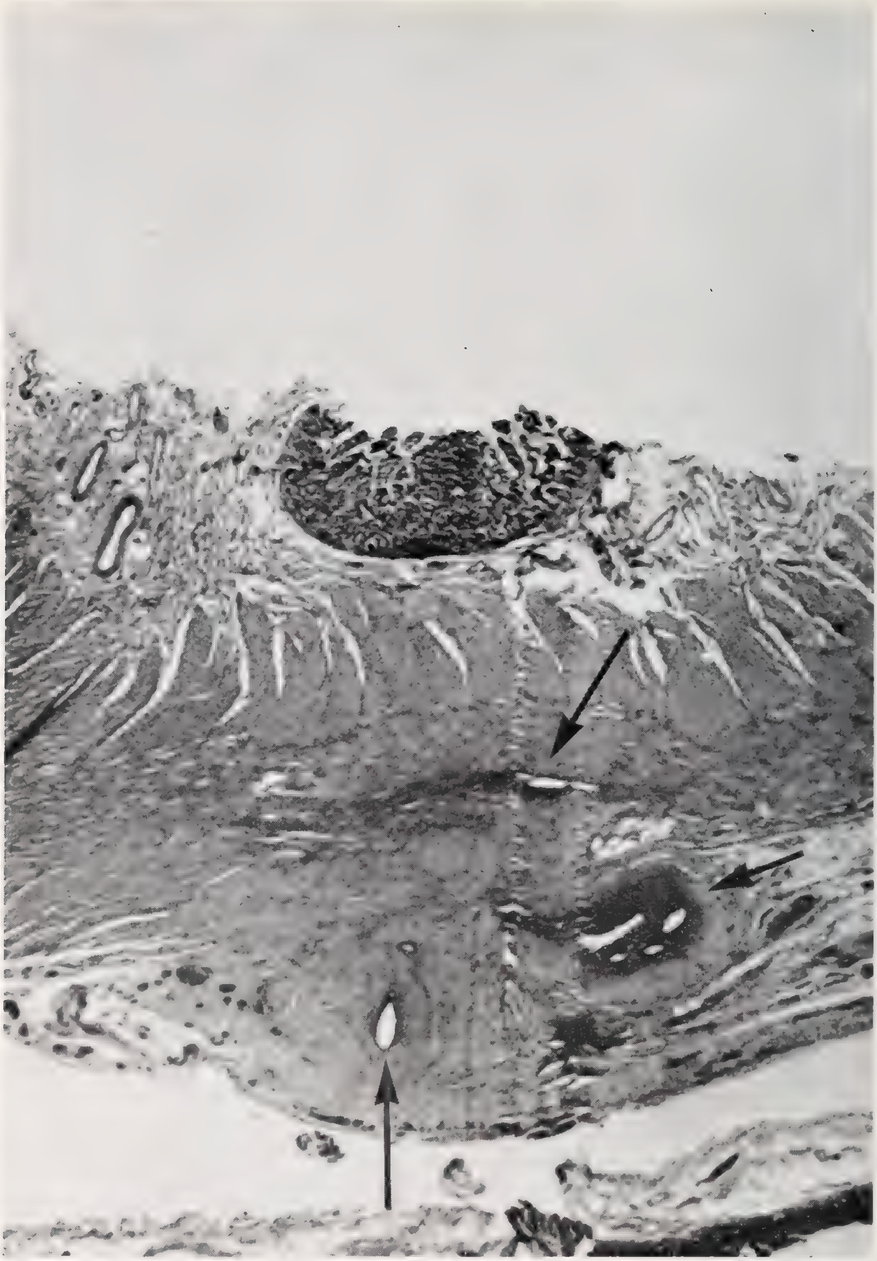

FIG. 3. Section of ileum with subserosal and outer muscular deposits of hemorrhagic endometrium surrounded by stroma and fibrous reaction.

volvement of some portion of the intestinal tract in 12 percent (2). In most of the intestinal cases (85 percent) the pathology involved the rectum, rectosigmoid, sigmoid, or rectovaginal septum. The incidence in the small bowel was seven percent; this incidence is probably much higher since it is based only on the number of patients who were operated upon. It is likely that many endometriomas of the small bowel are overlooked unless the bowel is carefully examined during operations for pelvic endometriosis. The lesions in the small bowel are usually situated not more than 12 inches from the ileocecal junction. They sometimes occur more proximally and in many instances several constricted areas may be found. In one case recently reported a 2 cm subserosal endometrioma of the jejunum was excised during an operation for reconstruction of the common bile duct (3).

The endometrial lesions are at first subserosally located. With the passage of time and the repeated irritation of the hemorrhagic detritus during each menstrual period an ever widening layer of fibrosis occurs. In almost every case of ileal endometriosis which caused intestinal obstruction, there is demonstrable invasion of the muscularis (4). Several mechanisms have been described by which ileal endometriosis may lead to intestinal obstruction: kinking of the bowel due to fibrous adhesions secondary to extravasated blood, stenosis due to fibrous reaction around the deposits of endometriosis, volvulus due to adhesions, and intussusception (5). In the case herein presented the obstruction was due to the intramural desmoplastic reaction around the endometriosis. The involvement of the mesentery in this case is very unusual; we have not encountered any mention of mesenteric endometriosis in the literature. Rare complications of intestinal endometriosis are perforation and malignant transformation.

Clinical Considerations

Small intestinal endometriosis usually affects women in the child-bearing age. Some authors believe that women who are sexually dormant, whether married or single, are particularly susceptible; in this connection, it is to be noted that the case herein presented is a virgin (6). Most cases give a history of intestinal symptoms which are intermittent and associated with the onset of menstruation. At first this may take the form of lower abdominal pain and diarrhea which is believed to be associated with superficial bowel implants. Symptoms of low grade obstruction are exhibited by nausea, vomiting, and crampy pain at periods and are believed to be associated with deeper implants (2). Such symptoms are usually progressive and may go on for months to several years. Not infrequently the pain may be localized to the right lower quadrant and mimic appendicitis or regional ileitis. Many patients give a history of appendectomy or pelvic surgery without relief of symptoms and subsequently require surgery for the ileal endometriosis. A smaller number of patients present as surgical emergencies with acute intestinal obstruction manifested by intractable vomiting, severe periumbilical or epigastric pain, and distention.

The diagnosis of ileal endometriosis depends primarily on the threshold of suspicion. Only if the clinician is aware of the possibility will he take a full and searching clinical history; he will ask leading questions concerning dysmenorrhea, dyspareunia, infertility, and the menstrual periodicity of many intestinal symptoms. The absence of pelvic pathology does not rule out the possibility of ileal endometriosis since half of the cases which are operated do not reveal any endometriosis in the pelvis. On the other hand, women who undergo surgery for pelvic endometriosis may subsequently require another operation for intestinal obstruction because the ileal lesion was overlooked the first time. If radiographic investigation is performed before or during a menstrual period when the ileal endometrioma is engorged and larger, a positive demonstration of the lesion is more likely.

The preferred treatment for ileal endometriosis is a resection of the involved portion of ileum with end to end anastomosis. Castration without ileal resection has failed in several cases which required a second operation. Furthermore, since the diagnosis of an ileal endometrioma is difficult at the operating table, resection is preferable to make certain that the lesion is benign. Whether any concomitant surgery is performed for associated endometriomatous pelvic deposits or ovarian chocolate cysts depends upon the age and condition of the patient. One can be radical if the patient is over 40, in good condition, and has had children.

Summary

A case of intestinal obstruction caused by ileal endometriosis is presented. The preoperative diagnosis is rarely made and the lesion is not often recognized at the operating table. The importance of clinical awareness and a full clinical history in making the diagnosis is emphasized.

The pathology, clinical features, and surgical treatment are discussed.

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The Management of Strabismic Amblyopia

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Amblyopia is a serious consequence of strabismus, wasting the functional capacity of what in most cases is otherwise an entirely normal eye. Proper management of the varieties of ocular misalignment is important to avoid amblyopia.

Properly aligned eyes make possible the integration of images transmitted separately to the brain by each fovea and by surrounding retinal elements. Similar retinal images are required. When these are not present early in life, one or another type of amblyopia will develop. Von Noorden (1) has recently presented a revised classification of amblyopia, the essence of which is to distinguish between visual loss (without a retinal lesion) caused by insufficient retinal stimulation, such as might be seen in severe congenital ptosis or complete cataract, and visual loss caused by active inhibition of images from one retina when the visual cortex is presented simultaneously with conflicting information. This latter condition is seen in anisometropia, where identical images of different optical quality, and therefore of different attention value, are formed. It is also seen in strabismus where, due to misalignment of the visual axes, object rays falling on the fovea of one eye strike a non-foveal "point" on the other, yielding two images of this object localized separately in space. In individuals possessing fusion capacity, such images can often be perceptually superimposed and integrated, requiring a reorientation of localization values of normally noncorresponding retinal areas in the two eyes (anomalous retinal correspondence or ARC). At other times, or in other individuals faced with this visual dilemma, suppression of inhibition of the second image occurs.

Far more important is that the fovea of the deviated eye forms an image of a different object. The nature of central binocular vision is such that dissimilar images cannot be superimposed and simultaneously seen; the only available adaptation is suppression (2). For intermittent misalignments, such sensory consequences are facultative and disappear when the eyes are in the straight position or when binocular viewing is interrupted. In a constant deviation, this suppression may become obligatory and continue to exist even in monocular seeing circumstances as reduced visual acuity. Von Noorden (1) has emphasized that the term *amblyopia ex anopsia,* which implies deprivation, should not be applied to functional visual loss due to this active inhibition.

It should be mentioned at this point that anisometropia (unequal refractive errors) is often found in association with strabismus, and in this situation amblyopia is common and tends to be quite resistant to treatment. It is difficult to assess the relative etiologic contributions of anisometropia and of strabismus to the amblyopia in such cases, or to know whether the amblyopia is the cause of

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the misalignment. It is probably best to say that if anisometropic amblyopia can affect binocular position, it would be in converting a latent misalignment to a manifest squint, by obstructing the exercise of the compensating fusional vergence.

Although the basic fusion-free position of the eyes is not determined by sensory factors, what keeps eyes straight in everyday seeing is the exercise of fusion under ordinary stresses (i.e., with sufficient amplitudes). Well-developed vision in each eye promotes this and since proper alignment favors simultaneous foveal stimulation, the interests of continued good vision are served by straight eyes.

Ideally, all children should receive a complete eye examination by age two years (preferably earlier), and this should include determination of the refractive error under cycloplegia. Remember that the desirable findings of well-formed ocular structures and proper alignment are not assurance against decreased acuity caused by a high refractive error in one or both eyes.

The remainder of this discussion will emphasize the detection and management of strabismic amblyopia, this variety being both preventable and reversible when such efforts are timely.

Diagnosis

In the very young child, one must rely exclusively on objective criteria, of which the most valuable are the ability to fixate and to continue to fixate an object of interest. In the strabismic child, the presence or absence of a movement to take up fixation by the formerly covered eye is rather easily observed. It is generally preferable to employ a target at close range to coincide with the young child's range of visual interest. Moreover, since this information is generally sought prior to the obtaining of information about the refractive error, diminished visual interest due to a possible uncorrected myopia is avoided.

A helpful refinement in the observation of consecutive monocular fixation ability is for the examiner to make several small, rapid displacements of the hand-held fixation object, observing whether refixation ("chasing") is smooth and prompt or unsteady and slow. This is roughly comparable to employing the more sophisticated tests, such as using the visuscope which, of course, is not practical in the youngest age groups.

An immediate return to fixation by one eye after its cover has been removed is evidence that acuity is higher in the preferred eye although the degree of preference is not known. Where evasive movements or actual pushing away of the occluder is repeatedly done, the eye being required to fixate is usually at a severe disadvantage. The use of graded optokinetic drum stripes has been investigated as a means of quantitative visual acuity determination, but understandably enjoys no popularity in clinical practice.

The least distracting and threatening form of occlusion to the young child is the examiner's thumb. For targets, infants generally respond well to bright or animated objects. The Worth 4-dot flashlight is a most valuable attention-getter for the infant, especially when repeatedly flashed on and off. Its multiple elements provide visual detail superior to that of the ordinary penlight. For the slightly older but still pre-literate child, picture targets are useful. It is helpful to retain the child's interest by asking questions such as, "Is there a worm in the bird's mouth?" or "Is the cat wearing earmuffs?", rather than merely to request that the child look at the picture.

The phenomenon of cross-fixation as the explanation for the apparent bilateral abduction weakness of a congenitally esotropic baby is well known. Less often discussed is that unilateral cross-fixation, in which the eye that fixates across the nose continues to track the object of regard into its field of *ab*duction, is a valuable clue to its being the preferred eye. This phenomenon should not be taken to indicate unilateral abduction palsy in an otherwise neurologically normal baby.

Employing maneuvers such as these, we can characterize fixation behavior as good, apparently central, and either maintained or not maintained depending on whether fixation immediately and repeatedly shifts back to the just-uncovered eye. Poorer grades of fixation are described as wandering, visibly eccentric, or at times as no fixation at all. While the range of visual acuities represented by each grade overlaps the range of other grades in any one individual, a difference is a valid comparison of the visual ability of the two eyes, and can be used as an indication of amblyopia.

For the older child, Snellen-graded letters, numbers, Landolt rings, tumbled E's, and pictures have all been employed in visual acuity testing. It is well known but worth repeating again that separation difficulty is a characteristic of the amblyopic eye and that amblyopia can be masked if isolated optotypes are presented. A difference of two or more lines in comparative visual acuity may be overlooked unless groups of symbols are employed in testing.

Other methods of detecting amblyopia in a clinical setting include more sophisticated evaluations of fixation behavior than those already discussed. The visuscope is a modified ophthalmoscope which projects the shadow of a fixated target in the instrument onto a location on the retina which can be observed and defined as foveal, parafoveal, paramacular, and peripheral or some similar classification. Fixation loci other than foveal are referred to as eccentric and can further be characterized as steady or unsteady. Care must be taken to employ low illumination and correctly to differentiate what are often fine oscillations around a constant center, from unsteadiness. It is of additional help to make several small displacements of the location of the target and note the reproducibility of the site used for refixation, similar to the chasing phenomenon already described.

Haidinger brushes are based on an entoptic phenomenon originating in Henle's layer of the retina, only in the foveal area. The patient sees what is usually described as a rotating bundle of wheat or a spinning propeller, whose hub corresponds to the fovea. Since only the fovea can generate the brush, comparison of the location of the center of rotation with a fixed point that the patient is requested to view in the same field, indicates whether the point is being foveally fixated.

These two methods, especially when both eyes are tested and compared, are based on the observation that while some amblyopic eyes retain foveal fixation in monocular seeing, eccentricity or imprecise fixation is a frequent accompaniment of amblyopia, especially the variety generated by ocular misalignment. Both tests have received prominence by advocates of pleoptic therapy, in which the analysis and treatment of fixation anomalies plays so prominent a part. Most workers in strabismus find that reliable responses can be elicited only in subjects old enough to be tested with graded Snellen symbols and that these latter are quite reliable and very much easier to employ.

Management

No less important than the diagnosis of amblyopia is its treatment; by far the best is prophylaxis. This implies the early elimination of predisposing factors such as strabismus and anisometropia. Contact lens correction of unequal refractive errors has become more extensively employed in the past several years and under favorable circumstances can be commenced prior to age one year, with keratometry and trial fitting under general anesthesia, instructing of the responsible adult, and monitoring of both the visual acuity and the effect of the lens on the cornea. Occlusion, as will be discussed below, is usually required as adjunctive treatment. In response to a question frequently posed by parents, there is no age too early to examine either a straight or a cross-eyed child, including retinoscopy and ophthalmoscopy. It seems appropriate to stress that "orthophoria" should not be regarded as invariable indicating either the exercise of fusion or the presence of equal visual acuity since this rather poor term is applicable to a fusion-free position of the eyes in which the fixation axes might happen to intersect at the object of regard. This is not assurance against decreased acuity.

Likewise, undetected or untreated infantile glaucoma can generate some combination of ametropic and suppression amblyopia on the basis of corneal distortion and unequal refractive errors. Partial cataracts present a dilemma, since although it has been stated frequently that enough space exists around such an opacity to admit object rays, delayed removal of such an opacity will affect the acuity of central vision.

When amblyopia is present it is generally agreed that occlusion of the preferred eye is the treatment of choice. If necessary this can be initiated as early as six months of age. It should be remembered that although the majority of infantile strabismus cases have the ability to fixate alternately, this is not invariably so, particularly if there is coexisting anisometropia.

It is widespread practice to employ alternating occlusion on a nonamblyopic infantile strabismus patient and in some cases surgery is deliberately postponed for this purpose. I would suggest that it would be far better to eliminate the strabismus and encourage fusion as a deterrent to the development of amblyopia than to reinforce the habit of alternation. When correction of strabismus must be delayed due to overriding medical considerations, I have found it more convenient and no less prudent to observe an alternator at intervals of 2 to 3 months without occlusion. It is unlikely that amblyopia developing during such an interval will be resistant to subsequent treatment.

When occlusion is employed, initially it should be during all the child's waking hours. This generally means that the occluder must be worn directly on the face to discourage peeking. If acuity in the amblyopic eye is initially very poor, warning should be given that visual behavior is liable to be uncertain and attended by some degree of fear or unhappiness. This usually improves as the amblyopia lessens and can be used by the parents as an indication of success of the treatment.

It is essential that the ophthalmologist take a firm stand on the necessity for this usually unpopular measure and an optomistic outlook as to the expected result. Parents too frequently respond to the recommendation for glasses or occlusion with a very obvious negative reaction, which can be communicated to even a young child. If such an attitude is allowed to go unchallenged, the therapeutic regimen is in definite jeopardy of being ignored or only sporadically followed. One way to make this point, which also serves to instruct parents in the occlusion technique, is to demonstrate the application of the adhesive patch over the child's eye and to send him home with the patch in place, thereby insisting that the treatment begin immediately. The parents must be made to understand that no other measures can approach the success of occlusion and that full cooperation over what may be a prolonged period will be necessary.

The use of cycloplegic drugs as a substitute for occlusion is not likely to be successful unless the refractive error of the favored eye is in the high plus range. This measure should be reserved for patients who absolutely will not accept occlusion.

Occlusion of the preferred eye and a red filter over the amblyopic eye has been employed when there is eccentric fixation (3). The value of this technique has not been shown conclusively, but it must be kept in mind for cases not responsive to more conventional occlusion methods.

Inverse occlusion, namely occlusion of the amblyopic eye to break up eccentric fixation, enjoyed a period of popularity but has been shown by studies of Parks and Friendly (4), Von Noorden (5), and others to offer no consistent advantage, particularly in children below 4 years of age.

The following treatment guidelines have been found helpful:

1. When performance on an acuity test or improvement in fixation behavior show that maximum benefit has been obtained, reinforcement of the improvement is usually insured by part-time occlusion (usually half the child's waking hours) or by periods of intermittent full-time occlusion if there has been regression. This is often necessary through age 8 years or later.
2. Always start with full-time occlusion. Part-time measures should be considered only as reinforcing procedures.
3. It is well to keep in mind that one is treating, not a pair of eyes but an individual, and that even a needed full-time regimen must be relaxed occasionally to allow for such activities as swimming.
4. One must be mindful of the phenomenon of occlusion amblyopia (6) and

monitor the acuity of both eyes during treatment. Indicated below are the initial intervals until reevaluation that are safe in most instances:

Interval Until Reexamination after Initiation of Full-Time Occlusion

0–1 yr.	7 days
1–2 yrs.	10–14 days
2–3 yrs.	14–21 days
3+ yrs.	21–28 days

These are rough guidelines and can be reduced or exceeded depending upon the severity of the amblyopia. Intervals after this initial reevaluation are determined in a similar way. When only part-time occlusion is being employed, the intervals between reevaluations can be extended to several weeks.

5. In general, a total of three months of conscientious full-time occlusion of the preferred eye should elapse before the procedure is abandoned for lack of any improvement.

6. An initial improvement, on the other hand, calls for extension of the trial for a longer period before it is concluded that maximum possible benefit has been obtained.

7. An infant who does not rapidly improve with occlusion should be suspected of having organic retinal disease, and ophthalmoscopy should be repeated, under general anesthesia if necessary.

8. Whenever possible, treat and eliminate strabismic amblyopia prior to surgery. This will encourage the immediate exercise of binocular vision when the eyes have been realigned, if fusion capacity exists. If an orthoptics program is felt to be indicated, the opportunity for reinforcement between training sessions will be furthered if vision is maximal and occlusion is not required. However, the ophthalmologist must be alert to relapses, and reinstitute occlusion in the postoperative period if indicated.

9. The treatment of amblyopia is most successful up to age 4, regardless of whether fixation in the amblyopic eye is foveal or eccentric (4). It is probably best to give at least a short trial of occlusion to an amblyopic child of any age who has not previously had one, if school work will not suffer unduly. However, in my experience, occlusion first begun at school age has rarely proven effective if amblyopia is severe. The academic and psychological contraindications strongly underline the need for early detection and prevention of this condition.

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Diffuse Lymphosarcoma of the Kidneys Manifested Solely as Progressive Azotemia

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Introduction

Renal involvement in malignant lymphoma is well known and has been previously described (1–5). Since 1946, six cases of lymphosarcoma have been reported wherein renal failure was the predominant clinical feature (3, 6–10). The purpose of this report is to describe a case of lymphosarcoma, complicated by secondary cryptococcosis (11, 12), in which the sole manifestation was renal failure.

Case Report

A 64-year-old man was admitted in September 1968 to another hospital with anorexia and a weight loss of 30 pounds, weakness, intermittent abdominal pains, and peripheral edema of approximately six weeks' duration. He was found to be anemic. A bone marrow test was nondiagnostic. The blood urea nitrogen (BUN) was 54 mg/100 ml; sodium, 128 mEq/L; and potassium, 6.4 mEq/L. Urinary 17 keto and hydroxysteroids were within normal limits. A flat plate radiograph of the abdomen showed both kidneys to be nearly equal in length, the right and left measuring 13 cm and 12.5 cm respectively (Fig. 1). An intravenous pyelogram revealed no visualization. The upper GI series was unremarkable. The patient was started empirically on cortisone 35 mg and Florinef® 0.1 mg daily, with clinical improvement, an increase in serum sodium, and a concomitant drop in BUN. He was discharged at the end of September 1968 with the diagnosis of chronic pyelonephritis and possible adrenal insufficiency. Six weeks later, steroids were discontinued.

In late January 1969 he was readmitted complaining of anterior chest pain and weakness. The patient was dehydrated, no lymphadenopathy, hepatosplenomegaly nor abdominal masses were noted. The hematocrit was 35%, WBC 5000 with a shift to the left, BUN 120 mg/100 ml, blood sugar 106 mEq/L and CO_2 10 mEq/L. Urine analysis revealed a specific gravity of 1.006 and 1+ proteinuria. Urine cultures grew out significant numbers of colonies of Aerobacter aerogenes. Chest X-rays showed thickened pleura and enlarged cardiac silhouette. A left retrograde pyelogram showed elongation and stretching of the inferior calyx with the inferior pole of the kidney now reaching the iliac crest (Fig. 2). Right side ureteral catheterization could not be performed. Following the onset of rapid atrial flutter, the patient was digitalized. A pericardial rub developed; the BUN rose to 184 mg/100 ml and peritoneal dialysis was instituted. The BUN and potassium decreased to 35 mg/100 ml and 3.9 mEq/l respectively.

On February 2, 1969, the patient was transferred to the Mount Sinai Hospital Service at Elmhurst. He was in acute distress and severely dehydrated. The temperature was 98 F, pulse rate 100 with occasional irregularities, blood pressure supine 110/80 and sitting 90/55. Fundoscopy revealed benign arteriolar changes. No peripheral lymphadenopathy was noted. Rales were heard in the right midlung area. The heart sounds were muffled and a grade II/VI holosystolic murmur was heard at the apex. The abdomen was distended with a questionable mass palpated in the left flank and no evidence of ascites.

The ECG was within normal limits. A supine chest x-ray revealed a left midlung

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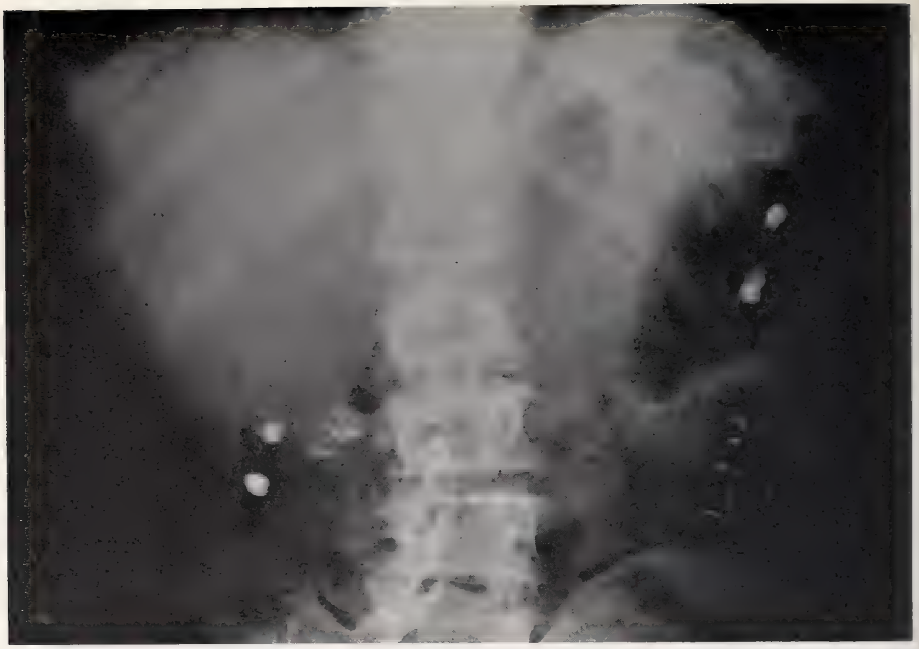

FIG. 1. This supine flat plate X-ray of the abdomen in September 1968, showed a 13cm long right kidney. The inferior pole of the left kidney was 2.5cm above the iliac crest while it measured 12.5cm long.

infiltrate and reticulations of the bases. An abdominal x-ray suggested a left renal shadow, extending below the iliac crest, which was larger than indicated on previous pyelograms. Laboratory data revealed: Hb 9.3 gm%; WBC 10,900; segmented 78; Staff 9, and lymphocytes 13. A clean catch urine revealed a specific gravity of 1.005, osmolality 250 Mosm/Kilo, 1+ proteinuria, coarse and fine granular casts, many bacteria, many RBC's per high power field, and a urinary Na content of 30 mEq/L. The BUN was 124 mg/100 ml, Na +136, mEq/L, Cl 100, mEq/L, CO_2 17 mEq/L, K+ 3.9 mEq/L, serum creatinine 10.3 mg/100 ml, uric acid 13 mg/100 ml, total proteins 5 gm/100 ml; and serum albumin 1.9 gm/100 ml.

The patient was started on ampicillin for a possible pneumonia and INH was added to the regimen. Despite rehydration with albumin and saline, urinary output remained fixed at 10–12 ml/hour. Twenty-four hours after admission, the sitting blood pressure rose to 110/70. On the third day, atrial flutter with a ventricular rate of 140 developed which was thought to be due to digitalis toxicity. The arrhythmia converted to sinus rhythm after intravenous administration of potassium chloride. Shortly after the initiation of peritoneal dialysis, the patient expired in cardiorespiratory arrest.

Postmortem Examination:

At autopsy, the heart was not enlarged. There were a few small, whitish granules in the epicardium and myocardium of the right ventricle and atrium. Both lungs weighed 1900 gms. There were many ill-defined consolidated patchy areas with a partly mucoid appearance, scattered in both lungs. The liver weighed 1400 gms and the spleen 180 gms. Grossly, the liver, gall bladder, spleen, pancreas, adrenal glands, thyroid gland, and parathyroid glands were unremarkable. The stomach showed a large, irregular, and ill-defined area of mucosal thickening along the greater curvature of the body. No abnormality was seen in the remainder of the gastrointestinal tract.

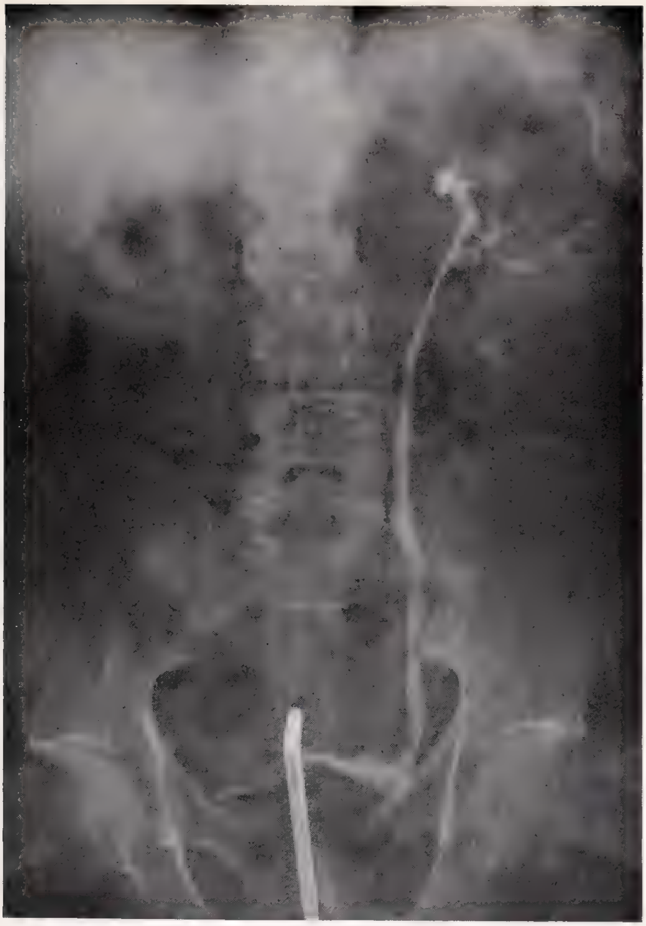

FIG. 2. This retrograde pyelogram in January 1969 showed elongation and stretching of the calyces with the inferior pole of the kidney now extending to the iliac crest.

The right kidney weighed 150 gms and the left 200 gms. The capsules were slightly thickened and stripped with little difficulty, leaving a pale and smooth surface. The cut surfaces of the left kidney showed a diffuse homogeneous "fish-flesh" appearance with complete loss of the cortico-medullary architecture. A portion of the cortico-medullary architecture was discernible in the right kidney. Both kidneys were rubbery in consistency. The calyces were small and compressed by tumor tissue. The remainder of the renal pelves and ureters appeared normal. The renal arteries and veins were patent. The lymph nodes in the renal hilum, pancreaticolineal and paraaortic regions were of normal size and consistency but their cut surfaces revealed replacement of normal tissue by the same homogeneous infiltrate as seen in the kidneys.

The pulmonary hilar and cervical lymph nodes were of normal size and contained mucoid material. The prostate gland was hypertrophied. The sternum and vertebrae showed the usual bone density and marrow. The brain was not examined.

Microscopically, the most striking changes were found in the kidneys. Almost the entire parenchyma was replaced by tumor tissue with only scattered glomeruli remaining (Fig. 3). The glomeruli showed focal collapse of capillaries with wrinkling of basement membranes

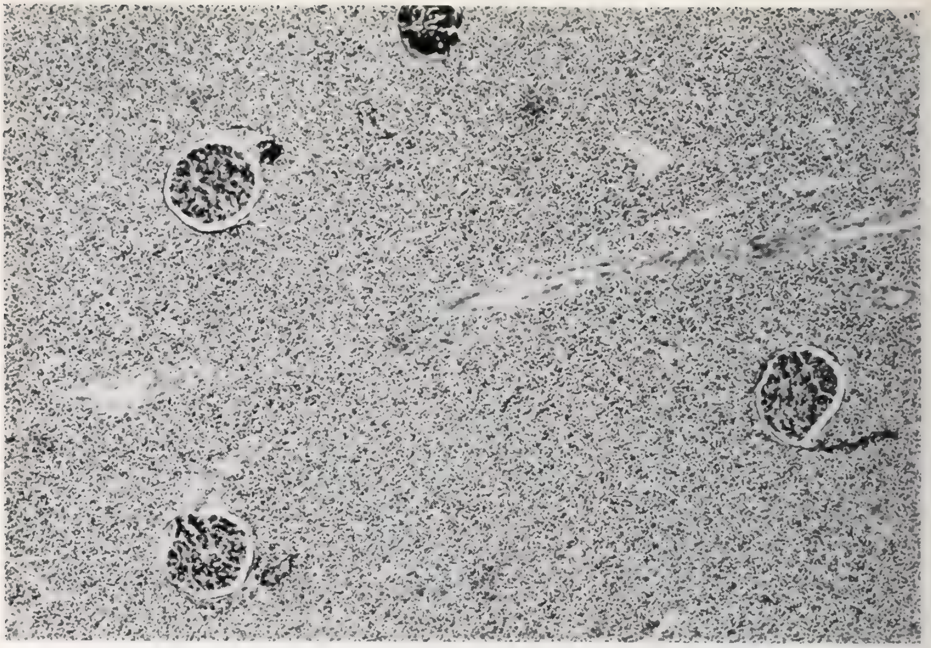

FIG. 3. Kidney, low power. The parenchyma is extensively replaced by tumor tissue with a few scattered glomeruli remaining (PAS stain 53× magnification).

with thickening of Bowman's capsules. The tubules were almost completely destroyed. Only in a few areas were there remnants of tubular structures which showed various degrees of atrophy and thickening of basement membranes. The tumor tissue was rather uniform and consisted of closely packed small cells with round or oval dark staining nuclei and scanty eosinophilic cytoplasm. The appearance of the tumor was consistent with lymphosarcoma of small cell type (Fig. 4).

Microscopically, the lung showed areas of granulomatous inflammation with collections of cryptococcal spores. The alveolar septae were thickened and infiltrated with lymphosarcomatous cells. Focal lymphosarcomatous infiltration was also seen in the epicardium and myocardium of the right ventricle and atrium, portal areas of the liver, mucosa and muscle layer of the stomach, mucosa of the urinary bladder, and bone marrow.

Comment

Renal involvement by lymphomas was found at autopsy to occur in as many as 61.9 percent of the cases (4). The antemortem evidence of renal lymphomatous disease was reported to be 10%, but death due to renal impairment occurred in only 0.5% of the cases reported (1, 2).

Renal failure may occur most often as a result of bilateral ureteral obstruction by enlarging retroperitoneal lymph nodes (14), uric acid calculus formation (15) or diffuse renal infiltration, as in our case. In our patient, the absence of peripheral lymphadenopathy, palpable abdominal or flank masses, and the lack of hematologic findings in the presence of progressive azotemia were the striking features. However, it was noted radiographically that there was progressive enlargement of the kidneys as shown in Figures 1 and 2. This suggested

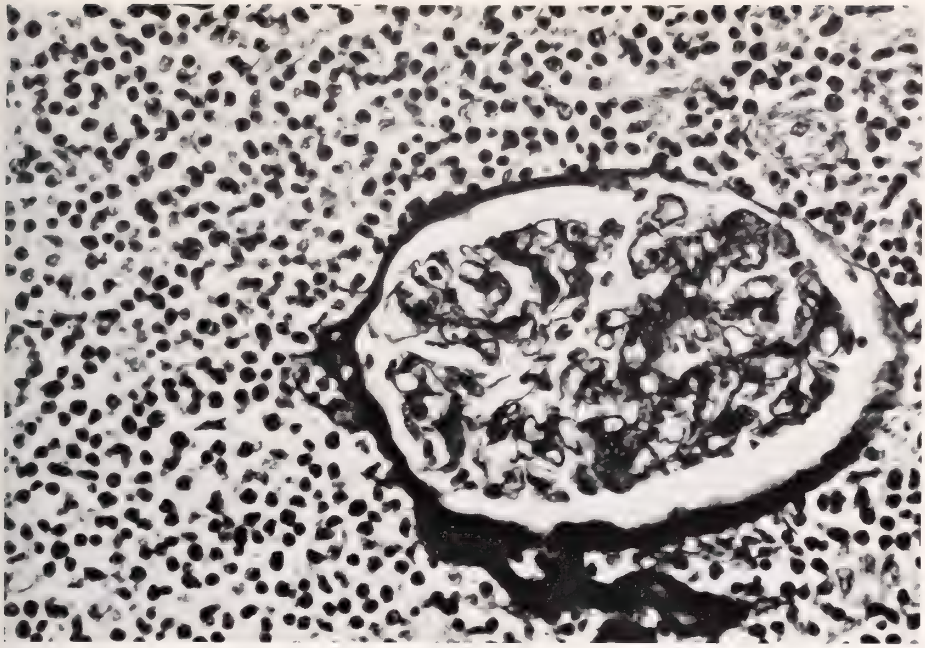

FIG. 4. Kidney, high power. The tumor is composed of uniform small lymphocytes. The glomerulus shows collapse of the capillaries with wrinkling of the basement membrane and thickening of Bowman's capsule. (PAS stain 525× magnification.)

possible renal parenchymal replacement by a tumor. The radiological features of renal lymphosarcoma have been previously described (1, 3, 13, 14). Enlarging kidney size, elongation and stretching of the calyces, and occasional ureteral dilatation, in the absence of a definite mass distorting the pyelogram, may be mistaken for a polycystic kidney (13).

Lymphosarcomatous involvement of the kidneys has been illustrated by Puente Duany (16) and classified by Gibson (14). It was found that single or multiple nodular infiltration is the most common renal involvement occurring in about 30 percent of patients with lymphosarcoma (1). Perirenal encompassment with (7, 12) and without (7, 11) renal invasion is less common while bilateral diffuse interstitial infiltration is rare. Seventeen cases with diffuse infiltration were collected by Puente Duany (16), and since that time six additional cases have been reported (3, 6, 7, 9, 10). The pertinent pathologic and clinical data comparing these six reported cases to our patient are summarized in Table I. All of these cases occurred in adults, although lymphosarcomatous infiltration had been reported to be peculiar to infancy (16). Abdominal masses and peripheral lymphadenopathy were noted in five patients. All of these patients had impaired renal function as well as symptoms and signs related to uremia. Although described by Kiely, Kretschmer, and Knoepp, primary lymphomatous involvement of the kidneys has never been definitely proven (4, 9, 17).

TABLE I

Diffuse Lymphosarcoma of the Kidneys: Clinical Data of the Seven Cases Reported Since 1946

Reference	Age Sex*	Palpable Abdominal Mass!	Peripheral Lymphadenopathy!	Chemistries NPN, BUN, Creatinine mg 100 ml**	Duration of Illness Months	Therapy	Weight of Kidneys Grams	Other Organ Involvement
9	56 M	+	−	NPN 111-254	6	None	4400	+
3	17 M	+	+	NPN 66-93	6	Radio Therapy	4770	+
7	65 M	+	+	BUN 92	4	None	1225	+
8	53 F	−	−	BUN 88-144 CR 5.6-10.8	14	None	1200	+
6	68 F	+	+	BUN 83	21	Radiotherapy Steroids	730	−
10	65 M	−	+	BUN 114	4	Radiotherapy Steroids	380	+
Authors	64 M	±	−	BUN 124 CR 10.3	4	Steroids	350	+

* M-Male; F-Female.

! + Presence; − absence; ±-questionable.

** NPN-nonprotein nitrogen; BUN-blood urea nitrogen; CR-creatinine.

The diagnosis of renal failure due to bilateral diffuse lymphosarcomatous involvement is difficult especially when the presenting complaints are only due to renal failure. Bilateral renal lymphomatous involvement should be considered as a possible etiologic factor in cases of renal failure with progressive renal enlargement.

Summary

A case of a 64-year old man with progressive azotemia due solely to lymphosarcomatous infiltration of the kidneys is presented. No peripheral lymphadenopathy nor abdominal masses were palpated. The major radiographic findings consisted of enlarging kidney size and elongation of the renal calyces. Tumor replacement of renal tissue was suspected because of the radiographic findings. An additional post-mortem finding was cryptococcal involvement of the lungs.

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Psychological Reactions to a Cardiac Monitor

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The constant monitoring of vital functions has saved many lives by leading to the immediate application of necessary treatment in Intensive Care Units. Studies (1–4) focusing on the intensive care situation and the threat of death in such units have suggested that the monitoring devices themselves may have a profound psychological impact.

As monitoring has become more a part of patient care—it actually is the sine qua non of intensive care—the medical staff has the natural tendency to consider it as part of the normal environment. To the patient the Intensive Care Unit, with its complicated equipment, can be frightening. On one hand, the patient feels observed and protected to the highest degree possible; he knows that he is in the unit precisely because he is in the greatest danger. But the entire surroundings, staff, and equipment can be upsetting. He wants to be there and be helped, but he also wants to leave for a calmer setting as an assurance that he is not in danger. It is often at the point of transfer that he becomes anxious. In our experience this rate of transient anxiety is quite high. Others (2) have not seen a high rate, but Klein et al (5) emphasize the transfer as a crisis point because of the danger of arrhythmia occurring as a manifestation of this anxiety.

The following report of the experiences of a patient in a coronary unit originally brought the problem to our attention and illustrates some of the reactions to be discussed.

> It was with a strange sense of relief that I entered the hospital and was wheeled into the Coronary Unit. The feeling of unease which had pervaded me from the start of my chest pain left as I actually went in and was put to bed. I was almost immediately struck by the air of competence and quiet confidence demonstrated by the nursing personnel who got me into bed and attached a continuous recording device to my chest, while someone on the other side of the bed inserted a continuous drip intravenous which stayed the five days or so I was in the Intensive Care Unit. The strangeness of my surroundings, encased as I was in a small cubicle with no sign of other patients nor of activity outside the cubicle window, did not strike me at first, since the feeling of rest and relaxation persisted.
>
> The feeling of confidence and competence was enhanced the second night when one of the electrodes came off as I shifted in bed. There was an immediate alarm, the whirring of machinery, and almost simultaneously the arrival of an attendant and a nurse followed shortly thereafter by a doctor. Fortunately for me the record which indicated a stoppage in asytole was only an artifact due to the coming off of the electrode, but it was to me an

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important demonstration of the quick response available should an emergency arise.

I was aware my symptoms were relatively minimal, yet there was always a concern that something was evolving of which I knew nothing. Going to sleep was a period of apprehension. Sleeping interfered with one's own vigilance and therefore anything could happen. The night after the electrode had fallen off, I awoke sometime during the early hours of the morning and looked up anxiously at the monitor to see, not if it were going, but really to see if *I* was going correctly. My feeling was, as I looked up, that if the machine indicated it, I was still alive, with the implication that, if the machine didn't indicate it, then I was in trouble or dead.

After five days I was transferred from the coronary unit to a private room in another part of the hospital. Once moved I realized how safe I had felt in the coronary unit, even though the quarters were cramped, for I felt alone and cut off from possible aid. I missed the constant monitoring. It was several more days before I really felt comfortable away from the close, protective enveloping atmosphere of the Intensive Care Unit. The enforced passivity, along with the very intensive care and the security of the constant monitoring served to allay the fear of something happening to the body's most vital organ. Being alone in the luxurious private room removed this very important safety factor and allowed for a degree of free range of fear and fantasy that could not be masked as was possible in the Intensive Care Unit.*

Method

Twenty-five patients were chosen at random from the Coronary Intensive Care Unit. The only criterion was an ability to speak English. There was no attempt to select patients by age, sex, or socioeconomic status. In addition ten patients were randomly selected from the Cardiac Surgery Intensive Care Unit, in order to evaluate both the role of the illness and the difference in units in the patients' reactions.

In the coronary unit we saw 19 men and six women, this ratio reflecting the higher frequency of myocardial infarction in men. The range in age was from 41 to 80 years. The surgical patients selected at random ranged in age from 21 to 80. There were five men and five women.

The interviewers introduced themselves as psychiatrists who were interested in the patients' reactions to their illness and treatment. Because of the medical situation, the interviews were kept relatively brief.

The coronary unit is an eight-bed ward divided into glass enclosed cubicles. The monitors are behind the patients who must turn to see them; at night the reflection of the lights can be seen by the patient on the glass wall. The prominent monitor features for the patient were an oscilloscope screen showing the electrocardiograph and a blinking light reflecting the heart beats. Dials showing the pulse rate or blood pressure were rather inconspicuous.

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* The patient's report as given to one of us (E.D.J.) has been put in chronological sequence for clarity.

The surgical unit is a long, open room with eight beds which can be separated by sliding screens. There is a monitor behind each patient at the bedside. In addition, there is evident a great deal of other equipment not seen on the coronary unit—respirators, drainage apparatus, and, at times, an audible beeper announcing the heart rate.

Findings

None of the patients spontaneously mentioned the monitor when telling of the care in the unit. It was, therefore, striking to see how willing they were to describe their reactions to it when asked direct questions.

Coronary Intensive Care Unit

In the coronary unit, 15 of the 25 patients spent a good deal of time observing the monitor. Of these, 9 watched the oscillograph, 4 watched the blinking pulse indicator, one watched both, and one, a practicing physician, followed the EKG writeout. One patient insisted that she never looked at the monitor, yet we observed her staring at it several times even during the interview, leading us to wonder whether others who said they never looked might, in reality, "monitor the monitor," without being aware of so doing. Several patients reported that they never noticed the apparatus although they expressed great interest in it when it was discussed. One patient worried a great deal about it as a potential source of electrocution while another extolled its value at length.

The reasons given by patients for watching the monitor ranged from "I have nothing else to do," "It's interesting," and "I like to see if there are any changes" (spoken by patients who clearly could not decipher the EKG picture on the oscillograph), to one man's comment "I like to see what a normal EKG looks like." This latter remark typifies the denial* so prevalent following myocardial infarction (4, 6). Seventeen patients showed a marked use of the denial mechanism in dealing with their illness. But seven of the deniers still watched the monitor and ten did not. They, like the man with the "normal EKG," constantly pointed out how they were not bothered by the monitor, as if seeking to reassure themselves. This latter group of deniers included two patients who "didn't know and didn't want to know" anything about the monitor, patients who "never notice it," those who vehemently insisted they were not bothered by the alarms triggered by vital sign problems or electrode failure, and an efficiency expert who dealt with the entire illness situation in terms of his expertise. For him the monitor was a cost-saving device and he became part of an efficient system. He didn't have anything to worry about because "my heart's in pretty good shape."

Fifteen of the patients praised the apparatus with such expressions as "fantastic," "wonderful," "great," "the most important part of my treatment," "it takes the place of seven nurses." Of these 15, twelve watched the apparatus, and three did not. However, one might question whether this praise expressed true feelings, since several patients came to this expression after being lukewarm at first. The peculiar dependent position of the patient in the Intensive Care Unit affects his responses. It is difficult to know how much is an expression of what he feels will please the doctor rather than a statement of his true feelings. The patient feels particularly vulnerable and dares not offend his medical attendants.

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* By denial we mean the inability to become consciously aware of some reality because the reality, and its implications, are too painful to tolerate.

Only one patient directly expressed fear of electrocution by the apparatus, and another two indirectly by saying "others must be afraid of electrocution but not me" and "it doesn't frighten you as long as you read about it before." However, consultation with the nursing staff showed that almost every patient revealed to the nurses a fear of electrocution when the devices were connected.* A patient may find it difficult to tell the doctors, "I don't know if I can trust your equipment." Since nurses are considered as agents of the doctors, and, therefore, not responsible for ordering the medical regimen, a patient can complain to the nurse because his being exposed to danger is not her fault. This observation taken in combination with a wish to present a favorable appearance to the doctors makes the results of these and other interviews open to question. Thus, when it is reported (2) that half of a group of patients are reassured by the monitor, and more than a third are neutral, one may doubt such easy categorization. It is more likely that the responses are complex and mixed, paralleling patients' mixed reactions to the Intensive Care Unit itself.

An interesting response to the device was seen in five patients, who watched the monitor to see if they "were still alive." Three patients expressed this magical expectation directly and two others did so in a roundabout, embarassed way. This was reminiscent of patients seen after heart surgery over the years who were monitored by an audible signal. Rarely could these patients sleep when the "beeper" was on. They would lie in bed listening to their hearts beat, fearing to fall asleep lest the "beeping" stop (7).

Seven of the patients, all deniers, had no idea of the function of the monitor. One even decided it was an x-ray. But most of the remaining patients could describe the monitor's functioning in an accurate way. Some did this with an obvious understanding while others seemed to parrot the information given them on admission. Three patients expressed the feeling that the monitor was just an important part of the entire intensive care milieu, and one of these stated that it was the most important part.

Three patients attributed special protective qualities to the device. One of this group felt that the monitor helped heal her heart and expressed a special feeling about it. She was a poor, struggling woman in her 50's who managed to put several children through college at the cost of great self-deprivation. Describing the monitor, she said, "It's part of me. At least for a while it's all mine. It protects me and somehow I feel it helps heal my heart." Yet, later, this woman spontaneously remarked, "I'm not at all bothered by the machine." She thus gratuitously revealed her anxiety about it by denying the negative feeling.

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* This may not be such an unusual reaction. A casual poll of colleagues, including cardiologists, revealed a frequent, embarrassing anxiety on being wired for an electrocardiogram. "I know it's irrational because I know in detail how the EKG is wired, yet I can't help worrying when the wires are attached."

This patient epitomizes the ambivalence felt by many about the monitor—it helps, yet it is upsetting. Most patients looked upon the monitor as helping by keeping an ever-vigilant eye upon them and thus guiding the doctors and nurses in their management. This patient showed the unusual feature of feeling actively helped—"it helps heal."

Surgical Intensive Care Unit

The patients in the surgical unit represented a different population than those in the coronary unit. The latter would usually be pain free after the first day or so, whereas the postoperative patients would suffer several days of serious discomfort and be surrounded by drains, resuscitators and other dramatic equipment besides the monitors. In addition, they were usually chronic cardiacs with a history of multiple hospitalizations for heart disease. The coronary patients were mainly patients with a first attack and little cardiac history.

Of the ten patients studied, five watched the monitor, four observing the oscillograph. One man observed the blinker since he was concerned about his heart rate, knowing he might eventually need a pacemaker. The reasons given for watching the oscillograph were evasive and vague. One patient clearly kept a careful watch on all the apparatuses, both at his bedside and connected to other patients. Everything fell into the category of "the monitor"—the drainage devices, the respirators, etc. For this patient, as for others who did not observe the equipment, there seemed no separation of the monitor from all the other devices. One patient looked for "irregularities in the lines," though she had no knowledge of the EKG. Another patient, a bright executive, claimed to have "read the P waves." When he developed complications he began to resent the machine. Further exploration revealed an unconscious resentment of his physicians with displacement onto the machine. Since the machine belonged to the doctors it was a natural target.

Six of the ten patients showed a prominent use of denial in dealing with the monitor. One woman who kept looking at the oscilloscope was asked how she liked it. She replied, "I don't hate it. It lets the doctors and nurses know what's going on." ("Do you like that?") "Well, I don't hate it."

Only one patient spoke about the monitor in glowing terms. He was the man concerned about his heart rate, and said that watching the monitor made him feel secure. No patient described watching the device to see if he "were alive."

Although some ambivalence was expressed, as with the woman who "didn't hate" the monitor, no patient expressed a concern with electrocution. Strikingly, in contrast with the coronary patients, it is a rare occurrence for a surgical patient to express this concern to the nurses.

In general, as noted above, the patients did not differentiate between the monitor which observed them and the devices which were actively used in the treatment, such as respirators, suction equipment, and drainage apparatus.

Alarms

An alarm was triggered whenever a vital sign fell from a normal range or, often, when an electrode became dislodged. These moments created stress situations of an extremely high order, evoking the defense mechanism of denial to the highest degree. An occasional patient described a sense of anxiety the first time the alarm rang, but most shrugged off the event. None related anxiety to the subsequent alarms. While the prompt response of the staff tends to calm the patient's fears and reinforces the sense of omnipresent care, we feel that the patient's calm attitude is a facade for a great deal of anxiety. This was illustrated to us when a false alarm sounded during an interview. There was an immediate dilation of the patient's pupils and a look of intense fear, but verbally there was a casual disclaimer of any emotional discomfort by the patient.

Discussion

There was a considerable difference in how the two groups of patients viewed the monitor. For the coronary group, isolated in individual booths, with very little active medical care, the monitor seemed the main focus of treatment. The patients extolled its virtues, and most tended to watch it at some length. In addition, the knowledge that their monitors were duplicated and observed in the nurses station enhanced their importance to the coronary patients. It seemed that for many the monitor was the main guardian of their continued existence and improvement. The machine took over the individual's own vigilance and could remain alert even while the patient slept. The reaction of looking to the monitor to see if one were still alive expresses both the anxiety felt by a coronary patient as to his imminent demise and his magical belief that the machine could tell better than himself what was occurring. The machine was thus both a safeguard and a danger in what it might reveal.

The surgical patients, on the other hand, were subjected to vigorous procedures—suctioning, encouragement to breathe deeply, and to ambulate. While half of them watched the monitor, they did not attribute the same importance to the machine as did the coronary group. They tended to lump all the devices in the Intensive Care Unit into the same category. Further, because of the staff's activity, they were not subjected to long, quiet, relatively isolated periods. This tended to make the medical and nursing ministrations the central issue, and the monitors themselves a relatively minor one. When the other devices are also considered, the total gadgetry, of course, looms larger in importance.

The preoccupation with the machine in the coronary patients needs further comment. Ten patients stared at the oscillograph, although it was obvious that none of them could understand its EKG tracing. While some were concerned with deciphering changes, most could give no specific reason for their interest. This keen interest may represent an attempt to bind anxiety relating to the experience of illness, by means of shifting concern from the damaged heart to the workings of the machine. The patient who saw the monitor in terms of an efficient technological unit expressed this by suggesting he was only a cog in a well-functioning system. If the system functioned, so did he.

The calming effect of the Intensive Care Unit is related to the ever-present ministrations of the nursing staff. The monitor aids in this sense of constant observation and reproduces, emotionally, the early mother-child relationship with the mother able to respond quickly to the infant's needs. The monitor is an omnipotent observer which bypasses the chance for human failure. Only as an infant can a person feel so protected. What could become a mechanized situation with the patient attached to electronic gadgetry, thus becomes an intimate, personal relationship. Because of its duplication of the early mother-child dyad, it becomes for the patient the apogee of magic. The physician who considers the monitor the height of applied science, must recognize the difference in viewpoint between patient and staff. Only when he recognizes this gulf will the physician be in a position to reassure the patient and thus help make his treatment more efficacious.

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UNUSUAL PROBLEMS IN SURGERY

Intussusception in Henoch-Schönlein's Purpura

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Intussusception is a rare complication of Henoch-Schönlein's purpura requiring prompt surgical correction. Because of the protean nature of the illness, difficulty may be encountered in establishing the diagnosis. The following report is an example of a successfully treated case.

Case Report

M.S. (EGH #522806). A four-year-old white male was admitted to the Elmhurst General Hospital on the sixth of February, 1970 because of malaise, weakness of the lower extremities, and lower back pain. These symptoms were antedated by twelve days of intermittent sore throat, fever, and headaches. There was no history of allergy to food, drugs, or other allergens. There was no significant family history of illness.

On admission the child was in no acute distress. His blood pressure was 110/60 mm of Hg, his pulse rate was 110 beats per minute, his temperature was 100.6°F rectally, and his respiratory rate 16 per minute. His tonsils were enlarged and congested. The heart and lungs were normal and the abdomen was scaphoid and not tender. There was marked tenderness over the lower spine, but no superficial evidence of inflammation. Examination of the skin revealed no abnormalities. The white blood cell count was 8,000/mm^3 with a normal differential count; the hematocrit was 35%, the erythrocyte sedimentation rate was 40 mm per hour. The urinalysis and serum electrolytes were normal.

The possibility of osteomyelitis of the spine was considered and the patient was given intravenous methicillin. The following day an urticarial rash appeared over both legs and the medication was stopped. Back pain subsided but the patient then complained of colicky abdominal pain which was accompanied by vomiting. Several hours later a petechial eruption was seen over both buttocks (Fig. 1) and the temperature rose to 101.8°F. Laboratory studies at this time included a white blood cell count of 12,000/mm^3, a normal urinalysis, a platelet count of 400,000/mm^3, a prothrombin time of 13.5 seconds (control of 11.5 seconds), and a partial thromboplastin time of 32 seconds.

During the next 24 hours, the patient complained of increasing abdominal pain. Abdominal distention became marked. His temperature was now 102.8°F. Plain roentgenograms of the abdomen (Fig. 2) revealed a high small bowel obstruction. A small bowel series was performed, but due to the slow passage of the barium the obstruction was not visualized. Although the initial films of the barium enema showed the colon to be normal, a late film revealed an intussusception in the distal ileum (Fig. 3). At this time the white blood cell count had increased to 31,500/mm^3 with a marked shift to the left and for the first time the urinalysis showed microscopic hematuria. An exploratory laparotomy was carried out under general anesthesia and an irreducible, gangrenous ileo-ileal intussusception was found two feet from the ileocecal valve (Fig. 4). The peritoneal cavity contained 200 cc of clear fluid. Several hematomas in the mesentery and small bowel wall were seen (Fig. 5). The small bowel was edematous and friable. Approximately 35 centimeters of bowel was resected and an end-to-end ileal anastomosis was performed. Examination of the surgical specimen showed the initiating point of the intussusception to be a submucosal hematoma (Fig. 6). Microscopic examination of the mesenteric vessels showed perivascular infiltration around the small arterioles (Fig. 7).

Following surgery the patient was given antibiotics and parenteral hydrocortisone. The

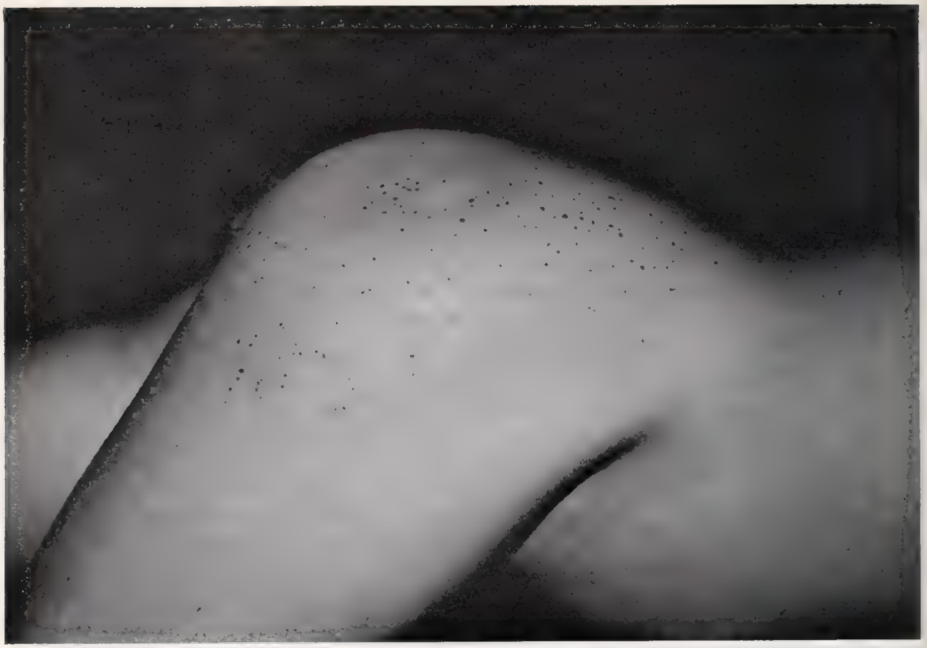

FIG. 1. Petechial lesions were limited to both buttocks.

early postoperative period was complicated by the appearance of ascites and a right pleural effusion. Hypertension (140/100 mm. Hg) was also noted. The hematuria, hypertension, and ascites subsided over the next three weeks. Steroids were gradually discontinued. The child was feeling well and completely asymptomatic when seen in the clinic one year later.

Discussion

Henoch-Schönlein's purpura is primarily a disease of childhood (1). Schönlein, in 1837 (2) first described the skin rash and joint involvement. In 1874, Henoch reported the cases of four children who had skin lesions associated with joint pains, colicky abdominal pain, and gastrointestinal bleeding (3).

The disease is considered to be an allergic perivasculitis of the small arteries (4, 5). Damage may range from minimal and reversible to severe injury with massive cellular exudations, edema, thrombosis, and infarction. The skin, joints, kidney, or gastrointestinal systems may be involved. The cutaneous lesion is characteristically a purpuric rash due to hemorrhage from the damaged vessels. Urticarial wheals or local edema may also occur. Joint manifestations include pain and swelling usually involving the knees and ankles (6). Gross or microscopic hematuria may occur. Late renal sequellae resemble the lesions of chronic glomerulonephritis. Visceral lesions consist of subserosal and submucosal hemorrhages with edema which may later cause obstruction or gangrene. Perforation and intussusception may then ensue (2).

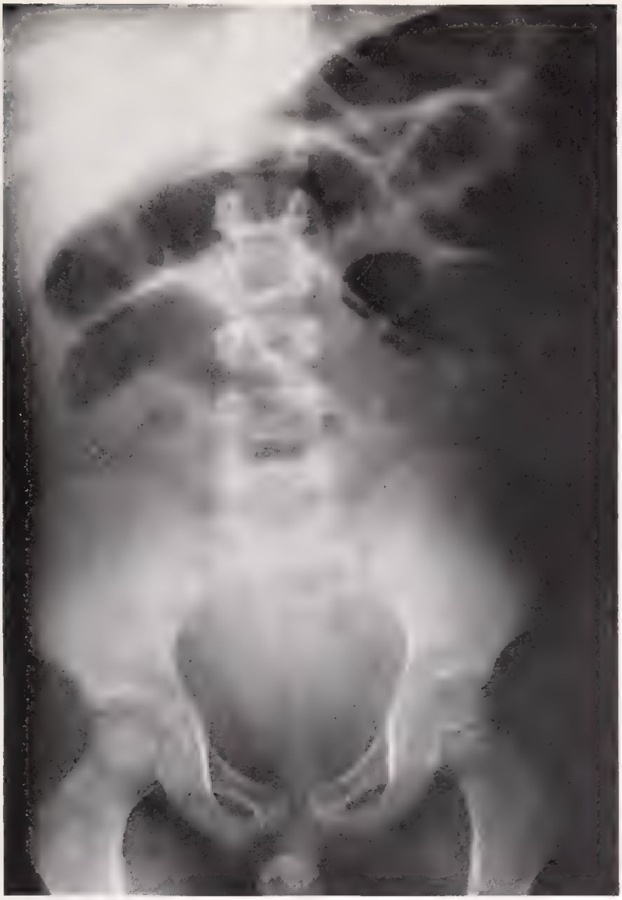

Fig. 2. Abdominal x-rays taken 48 hours after the onset of symptoms. There is evidence of small intestinal obstruction.

Crampy abdominal pain is extremely common in children with Henoch-Schönlein's purpura because of intramural intestinal bleeding. Vomiting, diarrhea, and gastrointestinal bleeding may occur. Symptoms, which may be multiple and of short duration, can involve any organ system. Exacerbations and remissions are frequently seen (6).

Intussusception is very uncommon; only sixty cases have been reported in the world literature (5–10). In a large series of patients with Henoch-Schönlein's purpura, the incidence of intussusception was six percent (6). In a combined series of over 1000 cases of intussusception in children none was due to Henoch-Schönlein's purpura. Intussusception usually occurs in the ileum. About 25 percent takes place at the ileocecal valve (6). The intussusception is usually caused by a submucosal hematoma which acts as a lead point (11).

The majority of patients with Henoch-Schönlein's purpura and abdominal

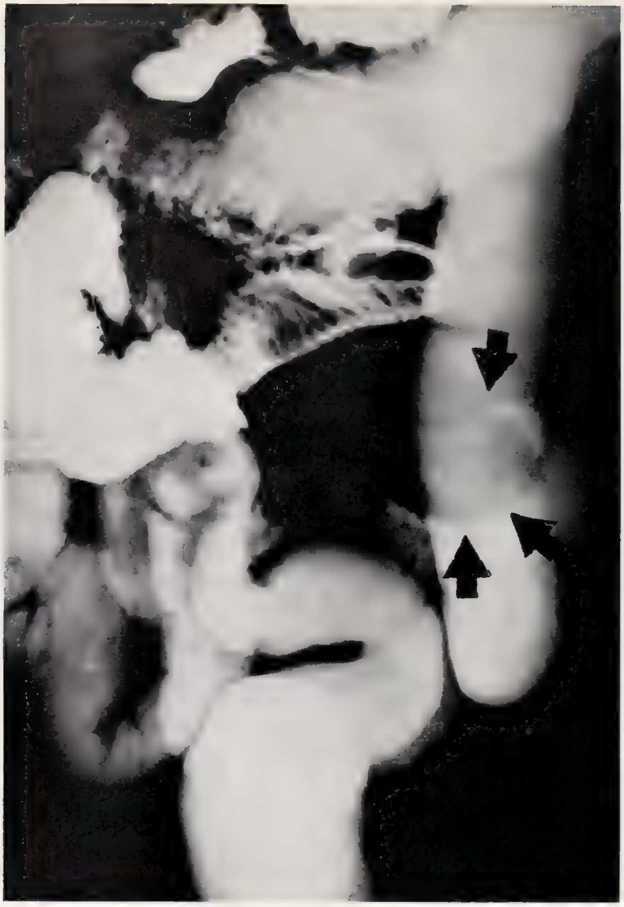

Fig. 3. Barium enema performed following a small bowel series. Note intussusception in distal ileum (arrows).

pain should be managed conservatively. Several clinical and laboratory signs are valuable in identifying the surgical candidate. While fever is usually present in Henoch-Schönlein's purpura, it is low grade and often irregular. When one encounters a patient with a high, persistent fever, a thorough search should be made for its cause. A mild leukocytosis is common in the disease (12). Marked leukocytosis should alert the physician. Although abdominal tenderness is often present, peritoneal signs such as rigidity and rebound tenderness rarely occur in the uncomplicated case (6). Further studies are indicated when any of the above signs are present. Plain roentgenograms of the abdomen are valuable in revealing intestinal obstruction or free air in the peritoneal cavity. A barium enema will often demonstrate the nature and site of the obstruction. If all studies prove negative the surgeon is fairly safe in adopting a watch-and-wait policy. Exploratory surgery is indicated if the studies are equivocal

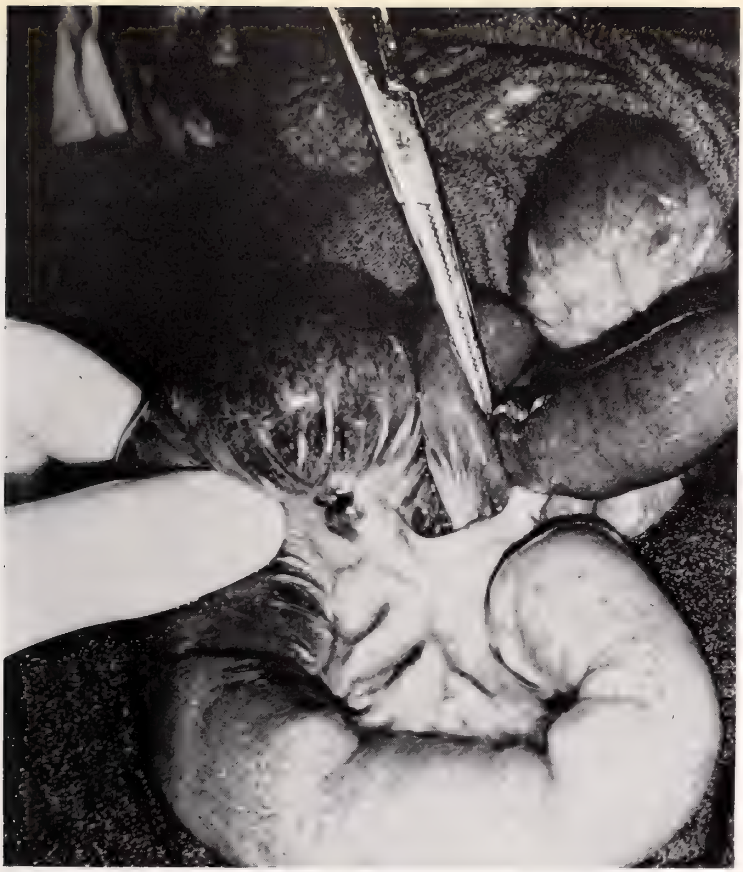

FIG. 4. Operative photograph. A gangrenous ileo-ileal intussusception was present. The clamp indicates the point of intussusception.

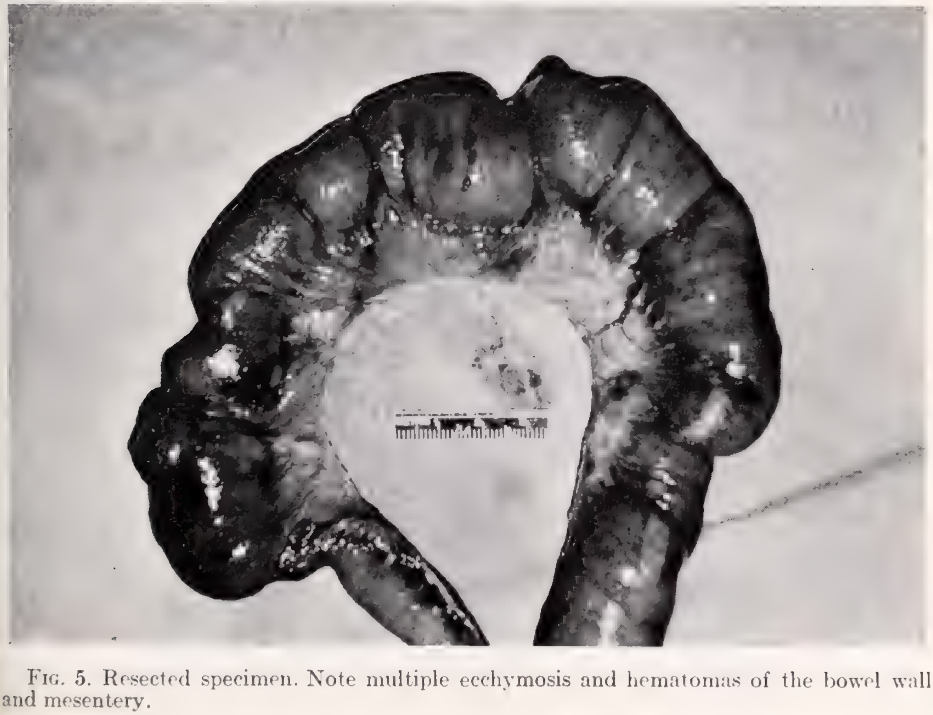

FIG. 5. Resected specimen. Note multiple ecchymosis and hematomas of the bowel wall and mesentery.

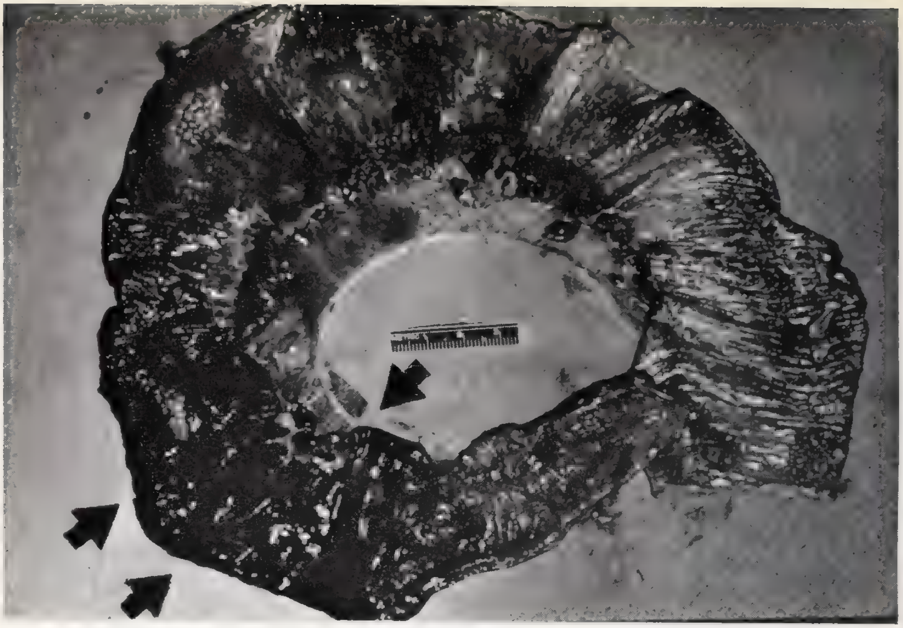

FIG. 6. Opened surgical specimen showing mucosal surface. Note hematoma which acted as the lead point of the intussusception.

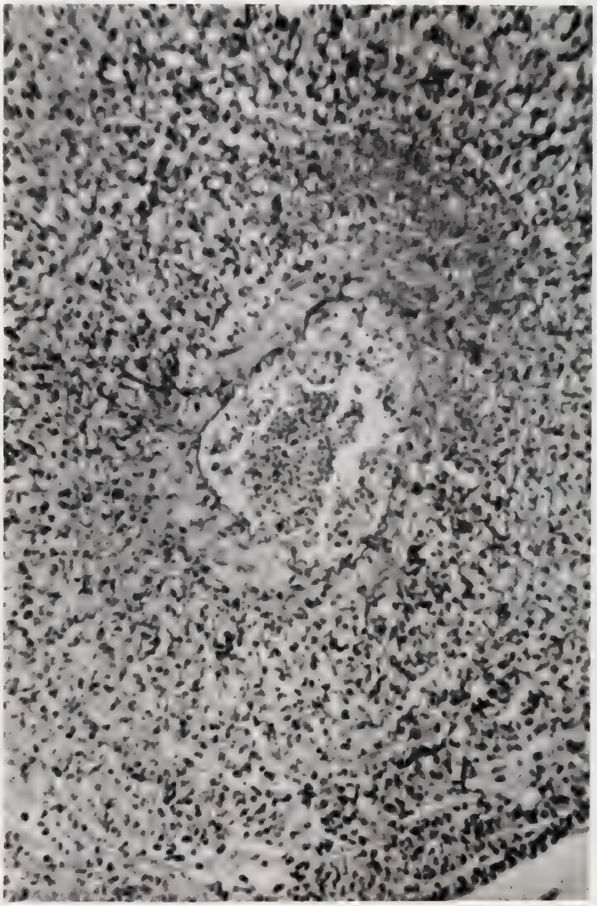

FIG. 7. Microscopic section of the mesentery showing perivacsular infiltration about a small arteriole.

and the patient's condition does not improve. It appears that a negative exploration does not alter the ultimate course of the disease (6).

Summary

The case of a child with intussusception as a complication of Henoch-Schönlein's purpura is presented and discussed.

Surgical complications resulting from Henoch-Schönlein's purpura are rare. Unless there are symptoms of impending peritonitis or bowel obstruction due to intussusception, conservative measures should be employed.

ROGER WOLFERT AND A. ROBERT BECK

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Clinico-Pathologic Conference

Scleroderma and an Acute Abdomen

Edited by
FRANKLIN M. KLION, M.D.

A 59-year-old white female was admitted to The Mount Sinai Hospital because of generalized weakness, progressive dysphagia, and abdominal pain. She had been in relatively good health until 20 years ago when she developed pain and a purplish discoloration of the digits of her upper extremities on exposure to cold. Sixteen and nine years prior to admission, she had pneumonia. After the latter illness, an x-ray of the chest was said to show interstitial fibrosis. Subsequently she noted increasing "dryness" of the skin, for which she was treated with topical estrogens. One year earlier, she underwent bilateral corneal grafts for corneal opacifications. Shortly afterwards she developed peripheral edema, difficulty in swallowing solid foods, and a persistent cough. She was admitted to The Mount Sinai Hospital.

The blood pressure was 130/80. There was tightness of the skin over the distal upper extremities with slight digital clubbing and pitting edema of the lower extremities. Esophageal motility studies demonstrated abnormally low resting pressure at the cardioesophageal sphincter and moderately low resting pressure in the proximal sphincter. Swallowing waves were of very low amplitude throughout the distal esophagus, while in the upper (striated) portion the waves were normal. These motility studies were interpreted as consistent with systemic sclerosis. An x-ray of the chest revealed prominent interstitial markings.

The hemoglobin was 12.4 G%, white blood cell count 16,000/mm^3, with 6% eosinophils. The erythrocyte sedimentation rate was 81 mm/hr. The total serum proteins were 6.9 G/100 ml, with 2.36% of gamma globulin. The blood urea nitrogen was normal. The urine contained a trace of protein. Latex fixation tests and LE preparations were negative. Serum antinuclear antibodies were absent. Pulmonary function studies showed abnormalities compatible with moderately advanced interstitial lung disease. An electrocardiogram showed a sinus tachycardia with premature atrial beats.

She was discharged on antibiotic therapy, but three months later was readmitted because of increasing dysphagia, weakness, and severe abdominal pain. The "tightness" of the skin over the hands and perioral areas was more prominent. Her abdomen was protuberant and tender to palpation. She was afebrile.

The hemoglobin was 10 G%. The white blood cell count was 36,000/mm^3 with a shift to the left. The erythrocyte sedimentation rate was 120 mm/hr. The BUN was 114 mg%, and serum creatinine was 6 mg%. The platelet count was 200 000/mm^3. Serum lactic dehydrogenase and glutamic oxaloacetic transaminases were mildly elevated. The stool was positive for occult blood. The urine contained moderate protein, and the sediment contained a few white blood cells and numerous red blood cells. A gastrointestinal series showed gas throughout the gastrointestinal tract, without evidence of mechanical obstruction or extraluminal air. A barium enema revealed pseudosacculations, increased secretions, and thickened haustra, compatible with systemic sclerosis.

Her abdomen became more distended and tender. The blood urea nitrogen rose to 219 mg%. A scan film of the abdomen revealed multiple irregular and narrowed loops of small bowel in parallel array, suggesting compromise of vasculature. At laparotomy there was marked hyperemic dilated small bowel with no definite gangrenous or perforated areas. Postoperatively her blood urea nitrogen continued to rise, her abdominal signs and symptoms progressed and she expired on the 10th hospital day.

Dr. Harry Spiera[*]: This Clinico-pathologic Conference is slightly different from most in that we are given the diagnosis. In fact, I was involved in her management during her initial admission.

She was a 59-year-old woman who developed typical Raynaud's phenomenon 20 years before admission. Raynaud's phenomenon is probably the most common presenting symptom of scleroderma. It has been suggested that there are differences between the Raynaud's phenomenon seen in scleroderma and in Raynaud's disease. The ischemia in scleroderma tends to be more intense, there is a higher incidence of ulceration and there are permanent ischemic changes in the digits. There are, however, many exceptions. In addition some investigators have claimed that the Raynaud's phenomenon in Raynaud's syndrome responds better to sympathectomy than does the Raynaud's phenomenon of scleroderma. The patients I have seen with scleroderma who have undergone sympathectomy for Raynaud's phenomenon have not been benefited, and I do not recommend sympathectomy for Raynaud's phenomenon in scleroderma.

Raynaud's phenomenon also is associated with other "connective tissue diseases," particularly systemic lupus, occasionally rheumatoid arthritis, and at times polymyositis and dermatomyositis.

This patient apparently did quite well for four years, when she had two bouts of pneumonia. Whether they were indeed pneumonia or whether she had already developed interstitial fibrosis is not known. In any event, she apparently recovered from these episodes, and subsequently was told she had interstitial fibrosis.

Scleroderma was considered for many years mainly a dermatologic disease because the most obvious manifestation was the hardness and tightness of the skin. The term, "progressive systemic sclerosis," on the other hand, draws attention to the systemic nature of the disease.

The vascular spasm of the small blood vessels and interstitial disease in the lungs were the predominant clinical features in this patient. Of 100 patients with typical features of scleroderma, a small percentage will have interstitial pulmonary disease with alveolar capillary block, manifested by a dry, hacking cough, dyspnea, tachypnea, cyanosis, pulmonary hypertension, cor pulmonale, and severe right-sided congestive heart failure. However, x-rays of the chest in the same 100 patients without dyspnea will show more radiologic features of interstitial fibrosis. They have sufficient pulmonary reserve so that symptoms do not result. If the remaining patients who have no chest x-ray changes are subjected to pulmonary function studies, a larger percentage would show impairment of diffusing capacity, using a single breath carbon monoxide method. Thus, the more sensitive the technique used, the more apparent is the systemic involvement.

Patients with rheumatoid arthritis also may develop interstitial fibrosis, and the Hamman-Rich syndrome. Pulmonary function studies in about 20 percent may show impaired diffusing capacity.

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In addition to Raynaud's phenomenon and interstitial lung disease, this patient later developed dryness of the skin which represented cutaneous involvement. She underwent bilateral corneal grafts for corneal opacifications. I searched the literature for information concerning corneal opacifications, but found no references. One could conjecture that in any connective tissue disease, certainly in lupus or in rheumatoid arthritis and ankylosing spondylitis, uveitis could lead to synechia, and to some degree of corneal opacification. I suspect that the corneal opacification might be related to a subclinical iritis or uveitis.

When she developed peripheral edema, the possibility of cor pulmonale with congestive right heart failure must be considered as well as renal disease. The renal disease of scleroderma is usually seen as rapidly progressing azotemia. The nephrotic syndrome with marked fluid retention with scleroderma is unusual. She then developed difficulty in swallowing foods and a persistent cough. The persistent cough, of course, is related to progression of the interstitial lung disease. Esophageal motility studies demonstrated low resting pressures at the cardioesophageal junction. I would like very briefly to call on Dr. Cohen who has investigated the abnormalities of esophageal motility in scleroderma.

*Dr. Bernard R. Cohen**: The sine qua non of esophageal involvement in systemic scleroderma is the absence of contractile activity in response to swallowing. For some unknown reasons, when scleroderma affects the musculature of the esophagus, only the smooth muscle if affected. The skeletal muscle is only involved if there is a coexistent polymyositis.

Multiple swallows in this patient showed a meager to absent pressure rise, in contrast to the pressure rises seen in normals. Esophageal motility studies are frequently helpful, since patients without skin changes and mild dysphagia may have significant esophageal involvement. Patients who were thought to have idiopathic pulmonary fibrosis may have sclerodermal changes in the esophagus. I have seen also a number of patients with scleroderma without skin changes who were studied for what appeared to be other illnesses. A few were admitted for dysphagia following repair of hiatus hernias. The repair of the hernia produced a tight hiatus, and the dysphagia was due to the lack of contractile activity in the esophagus.

Other gastrointestinal manifestations of scleroderma may be confused with other diseases. Dilatation of the second and third portions of the duodenum seen in scleroderma can mimic the picture of arteriomesenteric obstruction of the duodenum. The malabsorption syndrome may be a manifestation of scleroderma. A picture resembling regional enteritis with adhesions and chronic intestinal obstruction may mimic scleroderma.

Scleroderma, therefore, is not the only entity that can cause this type of physiological change in the esophagus. About three to five percent of patients with LE, rheumatoid arthritis, or periarteritis develop this type of esophageal dysfunction. Patients with diabetic neuropathy may at times also resemble the pattern seen with scleroderma. Age does not appear to be related. When esophageal motility is considered in conjunction with a composite clinical history, it can be of benefit.

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In summary, I would say that esophageal motility is a convenient physiological tool for diagnosis in patients who do not present with the typical features of scleroderma.

Dr. Spiera: Her disease started 20 years previously and demonstrates its insidious nature and the difficulties in dating the onset. This patient developed Raynaud's phenomenon 20 years previously. Let us suppose that at that time she was seen by a physician who established the diagnosis of scleroderma and treated her with either corticosteroids, antimalarial or immunosuppressive therapy. She would have been considered to have an excellent result, considering the initial slow progression of her disease.

We know very little about the natural history of the rate of progression of this disease. Some patients may have a very slow progression, and others can progress rapidly. Lacking knowledge of the natural history, institution of therapy may be a difficult decision. I saw this patient during her first admission. She complained bitterly of severe, lightning-like pain in her calves which was not related to effort or position. She had exquisite tenderness of the calf. Patients with scleroderma can have a synovitis which may resemble rheumatoid arthritis, except for a decreased tendency toward destructive joint disease. However, her pain was not that of synovitis.

I once had the opportunity to review the charts of 200 patients with scleroderma, and found that most patients with scleroderma are anemic. They do not have a striking elevation of the sedimentation rate unless there is another cause, and usually they do not have an elevated white count or hypergammaglobulinemia. In other words, if scleroderma is not part of the spectrum of diseases we call connective tissue diseases, it does not behave as an inflammatory process either. This patient had a high sedimentation rate, eosinophilia and an elevated gammaglobulinemia. Occasionally, hypergammaglobulinemia and an elevated sedimentation rate is seen in scleroderma. Eosinophilia is quite unusual. The severe myalgias, the fever and the eosinophilia make me suspect that the patient had a vasculitis. The skin and muscle biopsy, unfortunately, did not confirm this. I assume a large biopsy was taken, since I have seen many patients in whom very large biopsies showed a vasculitis in only one part of multiple sections.

She was discharged and readmitted three months later with increasing dysphagia, weakness, and severe abdominal pain. The clinical picture had changed entirely. She developed severe pain. She was anemic and had a markedly elevated white blood count. Her BUN, which was normal on her last admission, was 120 mg percent.

The renal disease that is classically described as occurring in scleroderma is clinically and pathologically similar to that seen in malignant hypertension. There is rapidly developing uremia and mild proteinuria. Pathologically the interlobular arteries are thickened. Fibrinoid degeneration is seen in the afferent arterioles. In contradistinction to lupus, where deposits of gammaglobulin and complement fixation are seen around the basal membrane, there are no deposits of immunogammaglobulin scleroderma. The renal disease of scleroderma is said to be precipitated by treatment with corticosteroids. This patient did not receive steroids but still she developed fulminating renal disease. One must be very critical, therefore, of cause and effect relationships based on clinical observations.

She was not hypertensive which is unusual in renal disease, although similar pathology may be found in the kidney whether or not the patient is hypertensive. At this point I would like to have Dr. Train discuss the radiographic findings.

*Dr. John Train**: The x-ray of the chest showed an interstitial pattern of fibrosis, predominantly in the bases, consistent with scleroderma.

The barium enema showed pseudosacculations on the filled and postevacuation film of the colon (Fig. 1). The mucosa in some areas was thickened and quite atypical of scleroderma, and would suggest some additional pathologic process. Several days after the barium enema, an obstructive series showed a loop of small bowel with abnormally thickened folds. A repeat film of the abdomen several days later revealed multiple loops of small bowel filled with gas. The walls of the bowel were thickened, narrowed, and irregular—quite typical of infarction. A retrograde pyelogram study revealed the pelvis and the left kidney to be normal.

Dr. Spiera: Thus, in addition to the rapidly progressive renal disease with hematuria and azotemia, she had scleroderma of the large and small bowel. The clinical picture, together with the severe myalgias, with the evidence of peripheral neuropathy, eosinophilia, fever, rapidly progressing renal disease, and now bowel infarcts, would be most consistent with a vasculitis involving the vessels of the mesentery and bowel.

Some patients with scleroderma have been described who died with a picture that mimicked polyarteritis nodosa. At autopsy these patients have a panarteritis involving all three layers of the blood vessels. Some patients with scleroderma have an aortitis, and some develop carotid artery occlusions.

Multiple muscle biopsy sections of patients with scleroderma examined with the electron microscope show capillary abnormalities which may be considered a microangiopathy. There is a decrease in the absolute number of capillaries per muscle area. The basement membrane of the capillaries are thickened. It may be that the disease which we call scleroderma has as part of its pathogenesis, a vascular disturbance which in some way leads to all the other consequences.

The association of scleroderma with other connective tissue diseases is a matter of semantics. We call this disease scleroderma because of certain characteristic clinical features, certain serologic abnormalities such as antinuclear antibodies, and to some extent certain characteristic histologic findings.

In summary, this patient had scleroderma, but died of a vasculitis which produced an infarct of the large bowel. I do not know whether the renal disease

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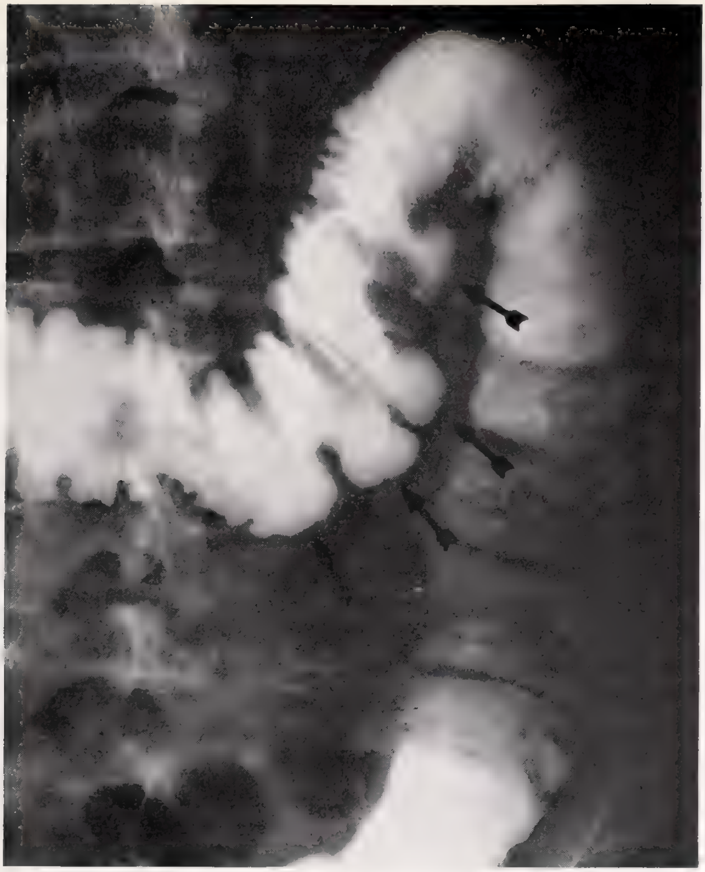

Fig. 1. (X-ray) Barium enema, performed ten days prior to death, reveals multiple pseudosacculations near splenic flexure (arrows), characteristic of scleroderma, as well as thickened irregular mucosal markings of transverse colon, suggesting early vascular compromise.

was renal disease of scleroderma, or a glomerulonephritis-like picture as seen in polyarteritis nodosa.

*Dr. Attila Toth**: The most striking finding at autopsy was a generalized vasculitis which involved small and medium-sized arteries and arterioles in varying stages of development. Two distinct types of vasculitis were present, one of them characterized by loose intima proliferation, mild media hypertrophy, and scattered perivascular inflammation. The late stage of this lesion showed complete obliteration of arteriolar lamina, with occasional vasculization (Figs. 2 and 3). The other distinct type of vascular alteration was demonstrated in small and medium sized arteries, and was most readily found in the kidneys and gastrointestinal tract (Fig. 4). The lesion was characterized by segmental or complete fibrinoid necrosis of the wall, profuse polymorphonuclear

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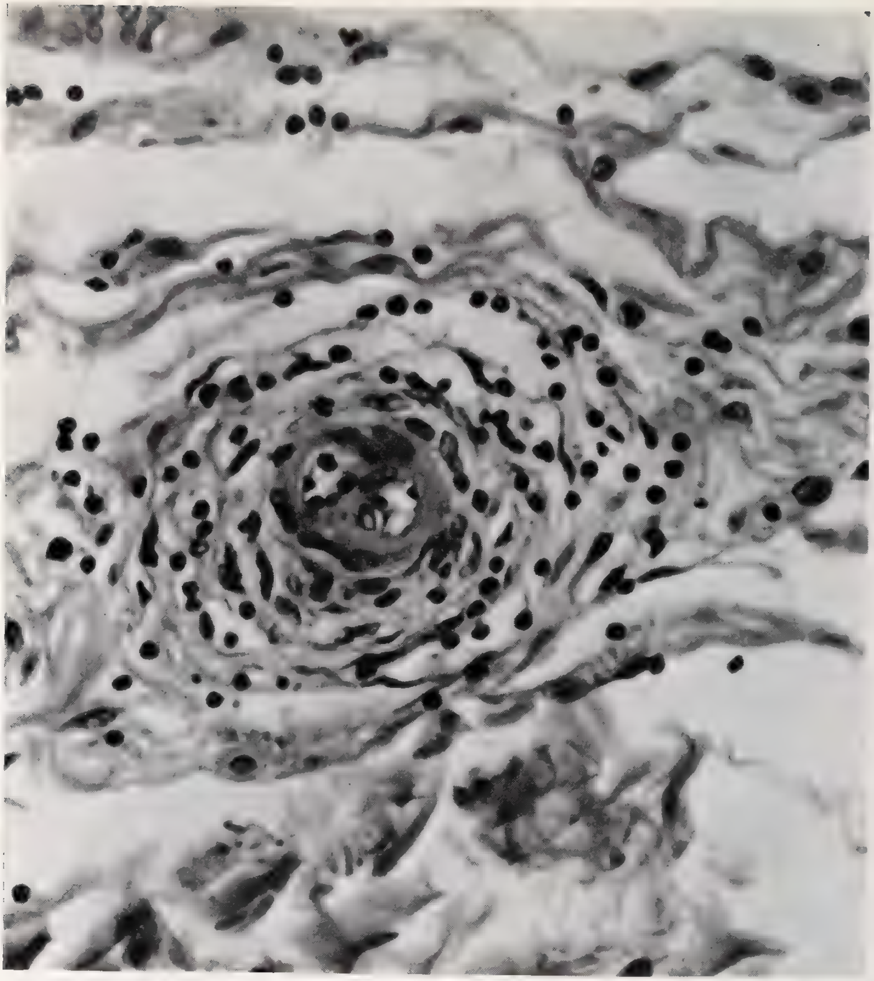

FIG. 2. Esophageal arteriole showing subintimal hyaline thickening with loose perivascular inflammation, typical of arteiolitis seen in scleroderma (HE × 200).

and eosinophilic inflammatory reaction involving all layers of the vessel wall. Advanced lesions which destroyed the elastica led to aneurysm formation and rupture of artery (Fig. 5). Occasionally, an intermixed form of the two types of vasculitis was also seen most prominently in the myocardium. Cryostat sections of arteries revealed 1 gG and β-1-C complement within the intima and along the elastica interna.

Another significant finding at autopsy was tightening and induration of skin over the anterior surface of the neck, over the chin with loss of wrinkling, and over the fingertips.

The lungs were normal in weight. The lower lobes were firmer than normal, the cut surface appeared dry, and the interstitial septa could be visualized with the naked eye. Microscopic examination of the lower lobes revealed diffuse

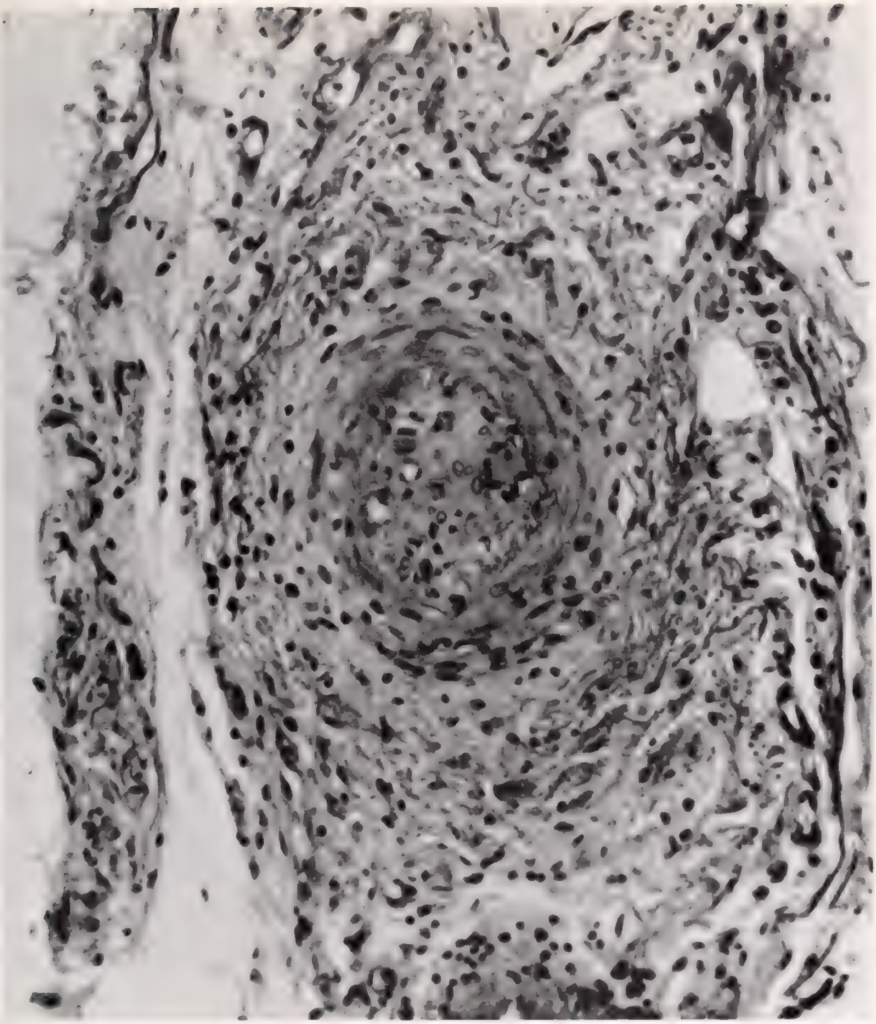

FIG. 3. Healed stage of scleroderma vasculitis showing obilteration of lumen of small esophageal artery by intimal proliferation with early recanalization (HE × 100).

interstitial fibrosis and diminution of the septal arterioles. A connective tissue stain showed deposition of thick collagen fibers and bronchiolization of the lumens.

The heart was of normal weight. There was no fluid in the epicardial sac. The right side of the heart showed marked dilatation, but was otherwise normal. The left side of the heart showed a mild hypertrophy. The bicuspid valve was thickened and calcified. There were numerous small foci of infarction in the myocardium, secondary to the obliterated arteries.

The liver revealed moderate periportal fibrosis and a vasculitis. The small mesenteric arteries showed similar changes resulting in segmental necrosis of bowel wall.

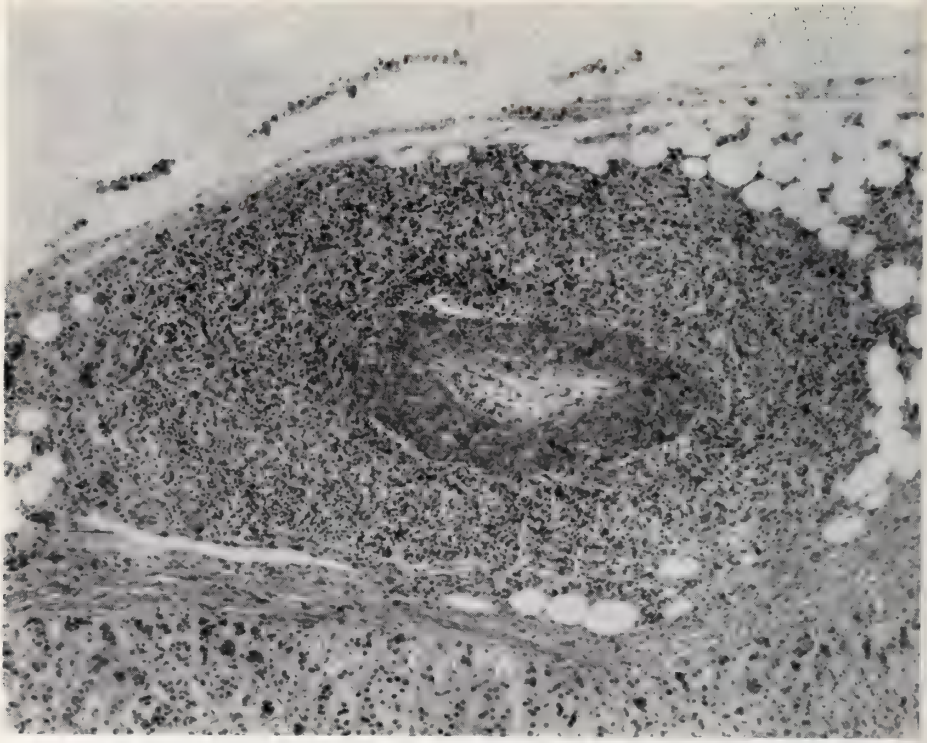

FIG. 4. Small periadrenal artery showing complete fibrinoid necrosis with acute panarteritis, indistinguishable from that seen in periarteritis nodosa (HE × 100).

The kidneys were normal in size. The cortex revealed numerous small, grayish yellow, elevated lesions which represented infarcts, secondary to occlusion of the interlobular arteries. Occasionally, aneurysm formation and rupture with hemorrhage were observed. Several glomeruli showed focal fibrinoid necrosis of the capillary tufts.

There are several groups of arteritis. The classical vascular lesion associated with scleroderma has been most recently summarized by Norton and Nardo (1), who suggested that the vasculature was the primary target organ in this disease. This lesion consists of mucoid intimal proliferation media hypertrophy, and a mild mononuclear infiltration of the adventitia. In addition, however, several authors reported periarteritis nodosa-like vascular lesions in scleroderma, with varying degrees of fibrinoid necrosis of vessel wall, aneurysm formation, and severe perivascular inflammation showing different stages of vascular injury (2–5). It seems, therefore, that besides the classical type of vasculitis of scleroderma, a fibrinoid-type necrotizing angiitis can represent also a distinct form of vascular injury of this disease. The present case—clinically and pathologically—was classical scleroderma as demonstrated by skin changes, abnormal esophageal motility pattern, Raynaud's phenomenon, and interstitial pulmonary fibrosis, and several vascular lesions most prominent

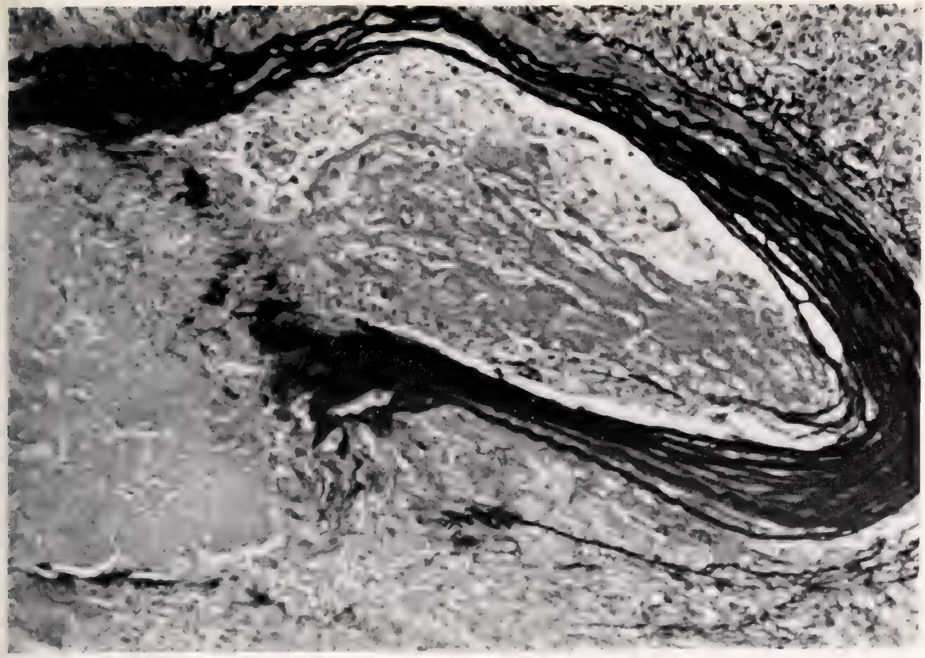

FIG. 5. Medium sized renal artery showing segmental necrosis with ruptured aneurysm (EVG × 100).

were necrotizing vasculitis. We believe that our case represents a case of scleroderma with an exceptionally severe necrotizing vasculitis which was more recent in origin. We cannot rule out the possibility of coincidental occurrence of two collagen diseases in one patient; however, we prefer to interpret it rather as a case of scleroderma with a prominent vasculitis component which is unusual but occasionally described in this disease.

Question: Since gammaglobulin is deposited in the lesions of periarteritis nodosa, can this be used in separating the two diseases?

Dr. Toth: The immunofluorescence studies at necropsy revealed γ-globulin and complement to be free within small arterioles, and γ-globulin within the inflammatory cells of the proliferative vascular lesions. Neither of these could be demonstrated to be free within the walls of the small- and medium-sized arteries undergoing acute fibrinoid necrosis. The few previous immunofluorescence studies of vascular lesions of scleroderma (6, 7) have failed to reveal γ-globulin or complement, although they have been reported in periarteritis nodosa (8, 9). I still feel that the limited number of these studies is not sufficient to make a generalized statement and criteria for differential diagnosis. If the vasculitis of scleroderma was accelerated by an unknown factor, it is possible that γ-globulins were trapped in the lesions without having any connection with the pathogenesis of the process.

Final Diagnosis:

SCLERODERMA TERMINATING AS PERIARTERITIS NODOSA.

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ASHER WINKELSTEIN, M.D.
1893–1972

In Memoriam

ASHER WINKELSTEIN, M.D.

1893–1972

Dr. Asher Winkelstein, a native of Syracuse, entered The Mount Sinai Hospital in 1917, serving a two and one-half year internship. He became Admitting Physician for two years and then went to Berlin for postgraduate studies in gastroenterology.

Upon his return, he enrolled as a clinical assistant in the outpatient department of gastroenterology. In 1926, he was appointed adjunct physician in medicine and chief of the gastrointestinal clinic. Eight years later was promoted to associate physician in gastroenterology. He was a dynamo of energy and impressed those about him with his diagnostic acumen and originality of ideas.

He was partially responsible for the development of the department of gastrointestinal physiology through grants obtained from the Altman Foundation. It was through his untiring efforts that a firm basis was laid for the department of gastroenterology.

Beyond his hospital and clinic responsibilities and ever-increasing private practice, he still found time to engage in research. He developed the milk drip treatment for duodenal ulcer. His original observations on peptic esophagitis still remain a memorable landmark in this disease. He published over one hundred articles pertaining to his specialty and was the author of two outstanding books, *Outlines of Gastrointestinal Diseases,* and *The Modern Therapy of Peptic Ulcer.* As assistant clinical professor in medicine at Columbia University, he conducted postgraduate courses in his chosen field at Mount Sinai.

He was elected to Honorary Fellowship in the American Gastroenterological Association and numerous medical societies and medical faculties here and in other countries.

Following his retirement in 1955, he became consultant in gastroenterology. He continued his practice and traveled extensively throughout the world. His lectures were enthusiastically received. As the years passed, his reputation all over the world increased and he became universally recognized as one of the great creative gastroenterologists of his time. When Mount Sinai School of Medicine was established in 1968, he was made clinical professor of medicine.

Asher Winkelstein died May 30, 1972 of arteriosclerotic heart disease. His memory will ever be engraved in the hearts of his dear wife, Celia, his son Charles, and his daughter, Ellen. He will be remembered by his colleagues as an outstanding diagnostician, clinician, noted investigator, great teacher, true and loyal friend.

Ralph Colp, M.D.
for the
Editorial Board

The Central Nervous System and Cushing's Syndrome

DOROTHY T. KRIEGER, M.D.

Since Cushing's description (1) of the syndrome that bears his name, there has been considerable speculation with regard to its etiology in those instances unassociated with adrenal tumor. In his initial description Cushing ascribed the clinical manifestations as being secondary to a "polyglandular syndrome." Prior to his more definitive paper (2) suggesting pituitary basophilism as the primary etiology, there were several case reports of patients with clinical manifestations of Cushing's syndrome in which mention of either an associated chromophobe adenoma (3) or basophilic adenoma (4) was made, without any appreciation of their possible etiologic significance. It remained for Cushing to observe that "if the acidophilic adenomas of acromegaly inevitably cause hyperplasia not infrequently associated with actual adenomata of the adrenal cortex, it is reasonable to assume that basophilic adenomas may well enough do the same."

The concept of a primary pituitary etiology remained a dominant one until the 1940's. During this period it was felt that adrenocortical hyperfunction was the primary abnormality with pituitary changes being secondary manifestations (5 and 6). Such reasoning was based upon the observed adrenal "hyperresponsiveness" to exogenous ACTH in patients with Cushing's syndrome as well as the observation that hyalinization of pituitary basophilic cells could occur in the presence of excessive amounts of cortisol, whether of exogenous or endogenous origin.

Even at that time, the suggestion was put forth (7) on the basis of observed postmortem pathologic changes in the hypothalamic paraventricular nuclei of patients with Cushing's syndrome, that the central nervous system was the primary site of the pathology in this disease. Despite isolated case reports (7 and 8) of the association of Cushing's syndrome with intracranial disease, there was no widespread acceptance of this concept, in part perhaps due to the observation that corticosteroid administration could lead to similar hypothalamic histologic changes in the experimental animal (9).

In the late 1950's increased ACTH secretion resulting from pituitary hyperfunction was again postulated as the primary etiology in nontumourous Cushing's syndrome (10). This suggestion was also compatible with the observed therapeutic response in this condition to pituitary irradiation or extirpation (11 and 12). Such a suggestion was difficult to reconcile with the observations at that time that there was no demonstrable increase in blood ACTH levels in such patients with Cushing's syndrome (13). This, however, was clarified as a result of studies showing 1.) that the presence of normal levels of plasma ACTH was "inappropriate" in the face of elevated plasma cortisol levels (14);

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2.) that following bilateral adrenalectomy, patients with Cushing's syndrome receiving maintenance corticosteroid medication displayed greater elevation of plasma ACTH levels than patients either with Addison's disease or those undergoing adrenalectomy for other therapeutic reasons and maintained on similar doses of corticosteroids (15); and (3) that the elevated corticosteroid levels seen in patients with Cushing's syndrome could be reproduced if normal A.M. plasma levels of ACTH were maintained throughout the 24-hour period, that is, with absence of their normal circadian fall (16).

The question remaining at present is whether such hypersecretion of ACTH in patients with Cushing's syndrome is due to primary pituitary hyperfunction, or whether this is secondary to dysfunction of pathways now known to regulate ACTH release and secretion. The purpose of the present paper is threefold: 1.) to review the current status of the evidence with regard to the etiologic role of either the pituitary or the central nervous system in the genesis of Cushing's syndrome, with special emphasis on the role normally played by the central nervous system in the regulation of ACTH release; 2.) to assess observed abnormalities in corticosteroid and growth hormone regulation in Cushing's syndrome in the light of the known central nervous system regulation of these parameters; and 3.) to consider possible therapeutic approaches to Cushing's syndrome based upon such a concept of central nervous system dysfunction.

Evidence of Pituitary Pathology in Cushing's Syndrome

The approximate incidence of the various known etiologies of Cushing's syndrome is indicated in Table I. The actual incidence of pituitary tumor is probaby higher. Most of the reported cases of Cushing's syndrome associated with pituitary tumor have been detected either by radiologic evidence of sellar enlargement on routine skull films, or by the patient's exhibiting neurologic signs suggestive of a suprasellar lesion. In this latter group, despite such signs, a large number of patients originally do not manifest sellar enlargement when initially seen. It is reported that there is evidence of suprasellar extension in 26 per cent of patients with pituitary adenomata and Cushing's syndrome in contrast to 15 per cent of patients with nonfunctional chromophobe adenomata (17). Furthermore, in cases with subsequent postoperative histologic verification of a pituitary tumor, only 50 per cent of these showed sellar enlargment when initially seen (17). At autopsy, 40 per cent of cases of Cushing's syn-

TABLE I

Etiology of Cushing's Syndrome

Adrenal Hyperplasia	(c. 50–70%)
Nodular Adrenal Hyperplasia	rare
Adrenal Adenoma Adrenal Carcinoma	(c. 20–30%)
Pituitary adenoma	
—pre adrex	(c. 10%)
—post adrex	(c. 15–20%)
"Ectopic" Tumors	(150 cases by 1964)

drome unassociated with adrenal or ectopic tumor had pituitary adenomata (18) in one-third of the cases these were small basophilic adenomata, the remainder being chromophobe. Although the basophil cell is considered to be the site of production of ACTH (19) there is also evidence that the chromophobe cell is capable of active secretion (20).

There is thus ample pathologic support for evidence of pituitary pathology in cases of Cushing's syndrome associated with bilateral adrenal cortical hyperplasia. The question remains as to whether derangements in central nervous system control of ACTH can give rise to such pathology.

Central Nervous System Regulation of Pituitary Trophic Hormone Secretion

Central Nervous System Regulation of ACTH

The role of the central nervous system in the regulation of both ACTH synthesis and release under basal and stressful situations is now well accepted (21). This evidence has been obtained as a resultant of diverse approaches assessing the effect of central nervous system lesions and stimulation on ACTH release, the effect of disconnection of the pituitary from the central nervous system either through transplantation or pituitary stalk section, and by observing the effect of neural tissue on pituitary tissue culture production of ACTH. Such neural regulation is believed to be mediated via a corticotropin-releasing factor secreted by neural (presumably hypothalamic) cells which, upon reaching the anterior pituitary via the hypothalamic-pituitary portal venous system, leads to release and possibly synthesis of ACTH.

At present the chemical nature of such a releasing factor is not known (22). Material with potent corticotropin-releasing factor (CRF) activity has been isolated from hypothalamic and posterior pituitary extracts of various species. These have been characterized as α_1 and α_2 CRF and β CRF. α_2 CRF has a proposed amino acid sequence similar to that of α-MSH, α_1 CRF is also related structurally to α-MSH. (It should be noted that α-MSH structurally is identical to the first 13 amino acids comprising ACTH). β CRF, which by weight is 50 to 100 times more potent than αCRF, has a ring structure reminiscent of vasopressin, and appears to be comprised of 12 amino acids. The presence of a corticotropin-inhibiting factor of cortical origin has also been suggested (23) and this is further supported by the observation that hippocampal stimulation (24) leads to a drop in plasma corticosteroid levels to below basal values.

It is presumed that release of CRF by the (hypothalamic) neurosecretory cell is secondary to prior depolarization of such a cell. The occurrence of depolarization would be dependent upon the sum total of the effects of excitatory and inhibitory neurotransmitters converging upon the cell, in addition to the effect of local ionic concentration, pH, and other factors—all determining the threshold of excitability of the cell. It may well be that the locus of action of steroid feedback occurs at this level, since corticosteroids are known to alter thresholds of neural excitability (25). Other data, however, suggest that corticosteroids may alter the activity of more distant portions of the nervous system, efferent projections of which converge upon the CRF neurosecretory cell.

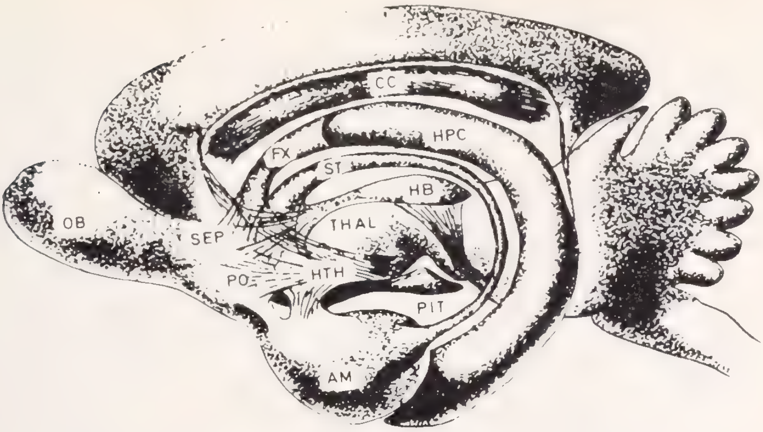

FIG. 1. The major components of the limbic system in the rat as seen in a schematized "phantom" diagram, projected on a sagittal plane. Most neocortical structures are not indicated, thus revealing the more "ancient" limbic components of the brain and their connections with the hypothalamus. Cerebellum and lower brain stem on the right. AM, amygdaloid complex; CC, corpus callosum; FX, fornix; HB, habenular complex; HPC, hippocampus complex; HTH, hypothalamus; OB, olfactory bulb; PIT, pituitary gland; PO, preoptic area; SEP, septum complex; ST, stria terminalis; THAL, thalamus. The medial forebrain bundle, olfactory tract, stria medullaris, and habenulo interpeduncular tract are sketched but not labelled. After de Groot (1965).

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In line with this, marked cytoplasmic and nuclear concentration of corticosteroid in amygdalar and hippocampal cells has been demonstrated (26).

This leads to a consideration of the neural inputs that can influence ACTH secretion. These are depicted in Figure 1 and indicated diagramatically in Figure 2. It is apparent that the hypothalamus serves as a "final common pathway" regulating ACTH release and secretion in response to a widespread input from diverse regions of the central nervous system.

Not all of these inputs may affect the same aspects of ACTH release, so that some may be involved in the maintenance of basal hormone levels, some may be involved in stress mediated hormonal responses, others in feedback regulation and still others in the regulation of hormonal circadian periodicity. For example, surgical interruption of anterior neural input into the hypothalamus disrupts circadian periodicity of adrenal corticosteroid levels but has no effect on adrenal cortical responses to stress, whereas interruption of posterior connections has a converse effect (27).

These different pathways may also utilize different neurotransmitters in activating the neurosecretory cell. Table II summarizes studies performed in our laboratory (28) indicating that different neurotransmitters have differential effects on ACTH release when implanted into a given area of the hypothalamus or limbic system, and that a given neurotransmitter has differential effects when implanted into different CNS areas. We have also shown that alteration in content of a given neurotransmitter (i.e., serotonin) will obliterate circadian

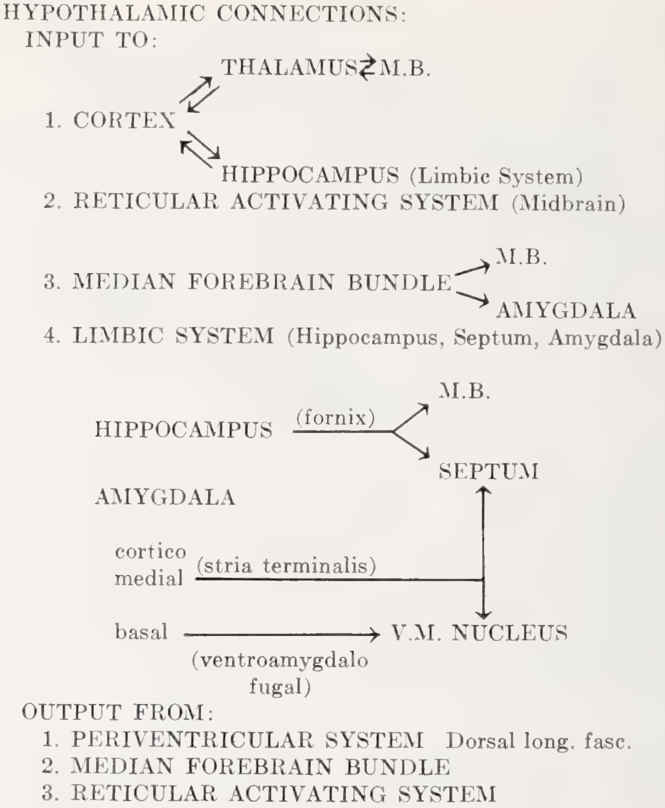
HYPOTHALAMIC CONNECTIONS:
INPUT TO:
THALAMUS ⇄ M.B.
1. CORTEX
HIPPOCAMPUS (Limbic System)
2. RETICULAR ACTIVATING SYSTEM (Midbrain)
M.B.
3. MEDIAN FOREBRAIN BUNDLE
AMYGDALA
4. LIMBIC SYSTEM (Hippocampus, Septum, Amygdala)
M.B.
HIPPOCAMPUS
(fornix)
SEPTUM
AMYGDALA
cortico medial
(stria terminalis)
basal
V.M. NUCLEUS
(ventroamygdalo fugal)
OUTPUT FROM:
1. PERIVENTRICULAR SYSTEM Dorsal long. fasc.
2. MEDIAN FOREBRAIN BUNDLE
3. RETICULAR ACTIVATING SYSTEM

FIG. 2. Summary of Major afferent and efferent connections of the hypothalamus.

TABLE II*

Effect of Implantation of Different Chemicals in Various C. N. S. Areas

	Carbachol†	Norepinephrine	GABA‡	Serotonin
Median Eminence	Positive	Positive	Positive	Positive
Mammillary Body	Positive	Positive	0	Negative
Posterior Hypothalamus	Positive	Negative	0	0
Hippocampus	Negative	Positive	Negative	Negative
Amygdala-lateral	Negative	Positive	Positive	Negative
-anterior	Positive	0	0	0
Septum-dorsal	Negative	Positive	Negative	Positive
-ventral	Negative	Negative	0	0

Positive indicates elevation of plasma 11-OHCS levels following implantation.

Negative indicates lack of elevation of plasma 11-OHCS levels following implantation.

0 Insufficient data.

* Reproduced with permission from Krieger, H. P. and Krieger, D. T., Am J Physiol 218(6): 1632, 1970.

† Carbachol is used as a long-acting prototype of acetylcholine.

‡ GABA (gamma-aminobutyric acid) is thought to be an inhibitory neurotransmitter.

periodicity of adrenal corticosteroid levels but have no effect on the adrenal cortical response to stress (29).

In this section mention has been made of the effect of both corticosteroid and neurotransmitters on the regulation of ACTH. An additional consideration is that these effects may not be mutually exclusive. There is evidence that alterations in corticosteroid levels can alter levels of brain amines (30) and it has already been noted above that alteration in brain amine levels can effect corticosteroid levels. It is possible, therefore, that in addition to the well-known feedback effect of target organ products on trophic hormone, one should consider an effect of the target hormone on neurotransmitter levels, thereby affecting trophic hormone release. One possible mechanism whereby cortisone may lower brain serotonin levels (31) is indicated in Figure 3, which is based upon the observation of corticosterone restoration of tryptophane hydroxylase levels after adrenalectomy.

From the above and other studies, it is therefore evident that in animals functional or anatomical alterations of the CNS may be associated with alteration in steroid feedback suppressability, altered circadian periodicity of adrenal corticosteroid levels, elevated corticosteroid levels, and altered corticosteroid responsiveness to stress. In the case of the limbic system, the current experimental findings are summarized in Table III. It can be seen that many of these findings are similar to the endocrine abnormalities seen in Cushing's syndrome.

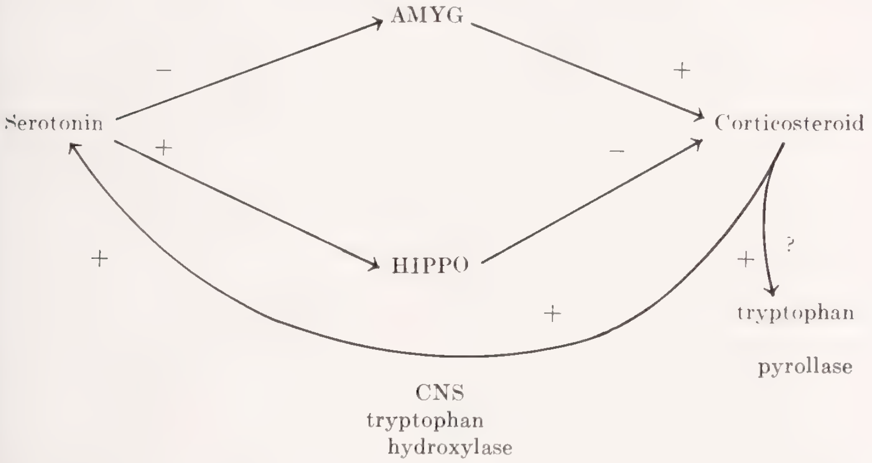

FIG. 3. Summary of experimental data indicating possible interrelationships between central nervous system serotonin and corticosteroid levels. AMYG = amygdala, HIPPO = hippocampus. Serotonin is inhibitory to amygdalar function, stimulatory to hippocampal function. Amygdalar stimulation increases, hippocampal stimulation depresses, adrenocortical output. Thereby increased serotonin levels might be expected to depress corticosteroid levels. In presence of lowered corticosteroid levels, there would be lack of induction of cerebral tryptophan hydroxylase, leading to lowered serotonin levels, increased amygdalar function, etc. The role of corticosteroid induction of tryptophan pyrollase, which would lead to enhanced metabolism of tryptophan by extra-CNS routes, thereby lowering CNS serotonin, is questionable, and would lead to effects opposite to those just described.

TABLE III

Summary of experimental observations indicating effects of alteration of amygdalar and hippocampal activity on adrenal cortical function

	Amygdala	Hippocampus
Stimulation	↑ Corticosteroid levels	↓ Corticosteroid levels ↓ Corticosteroid response to stress ↓ Amygdalar firing
Lesion	?Corticosteroid levels	↑ Corticosteroid levels ↑ Corticosteroid response to stress ↑ Circadian periodicity (fornix section)
Local Corticosteroid Implant	?Corticosteroid levels ↓ Corticosteroid response stress	↑ Circadian periodicity ↑ Corticosteroid response to stress
Local Serotonin Implant	↓ Corticosteroid levels	?Corticosteroid levels ↑ Hippocampal firing

This would lend credence to the hypothesis that localized neural dysfunction, local alteration in neurotransmitter content or ratios of inhibitory and excitatory neurotransmitters, or alteration of neurotransmitter sensitivity to steroid feedback might be possible factors in the etiology of nontumorous Cushing's syndrome.

Central Nervous System Role in Growth Hormone Regulation

As in the case of ACTH, there is central nervous system involvement in the secretion of other pituitary hormones. If the above postulate is correct that altered neurotransmitter content or feedback sensitivity explains the alterations in hypothalamic-pituitary adrenal function seen in patients with Cushing's syndrome, one might expect alterations in release of other pituitary hormones if similar pathways or transmitters are involved in their regulation. It is generally accepted that growth hormone secretion in response to hypoglycemia and other stresses is under central nervous system control (32) and that such stress induced rises are suppressed by alpha-adrenergic blocking agents (33). A sleep associated rise in plasma growth hormone levels also occurs in temporal relation with the electroencephalographic stage of slow-wave sleep (34) with considerable data indicating the presence of increased central nervous system serotonin levels in this state (35).

Endocrine Abnormalities in Cushing's Syndrome with regard to Possible Central Nervous System Role

A comparison of Tables III and IV shows many similarities between the alterations in hypothalamic-pituitary-adrenal function characterizing Cushing's syndrome and those seen following anatomic or pharmacologic manipulation of portions of the limbic system. Table IV indicates abnormalities in pituitary-adrenal and growth hormone responsiveness that we have noted in

TABLE IV

Characterization of Cushing's Syndrome (Adrenal Hyperplasia)

The major endocrine abnormalities in this syndrome are:
- (a) Increased adrenal cortical secretory rates
- (b) Increased urinary corticosteroid excretion
- (c) An abnormal, essentially flat, circadian periodicity of plasma corticosteroid and ACTH levels maintained at or above the normal peak level of circadian variation
- (d) Hyperresponsiveness to stimuli causing ACTH release, e.g., Metyrapone, Vasopressin
- (e) Elevated plasma ACTH levels (may not be seen in untreated state)
- (f) Lack of suppression of corticosteroid levels following doses of dexamethasone, which cause such suppression in normal subjects
- (g) A lack of responsiveness of plasma corticosteroid levels to exogenous "stress", (e.g., insulin hypoglycemia, piromen)

In view of these findings, two possible and perhaps related etiological factors leading to this syndrome are:
- (1) Elevation of the setpoint at which steroid levels are normally suppressed, (i.e., altered feedback)
- (2) Suppression of neural pathways which are normally inhibitory to ACTH release

patients with Cushing's syndrome whether active or in remission (36). The specific findings that suggest central nervous system involvement will now be considered.

With few exceptions (related to alterations in corticosteroid metabolism, conditions associated with lack of visual perception, or perhaps extreme stress), alterations in the normal circadian pattern of adrenal corticosteroid levels are seen only in cases of rather localized central nervous system disease (hypothalamic-limbic system) (37). The presence of increased plasma ACTH levels and their hyperresponsiveness to Metyrapone and vasopressin (used as a prototype of CRF) would indicate nonautonomous pituitary hyperfunction. Such hyperfunction might be secondary to increased stimulation by CRF—similar to the hyperresponsiveness of the adrenal cortex to exogenous ACTH seen in Cushing's syndrome, which is felt to be secondary to adrenal stimulation by increased amounts of endogenous ACTH. Although there is considerable controversy as to the locus of action of dexamethasone with regard to suppression of corticosteroid levels, there is a large body of evidence that would indicate that a major site is within the central nervous system (38), though there is some effect on the pituitary itself (39). Our previous studies reporting normal dexamethasone suppressability in three patients with hypothalamic disease (40) are not conclusive with regard to this problem, since no patients with known limbic system involvement were studied, and from animal studies, this appears to be the area of greatest steroid uptake (26).

"Stress" activation of the pituitary-adrenal axis is known to be mediated via central nervous system pathways (23). Table V summarizes the deficient corticosteroid response to both hypoglycemia and Piromen® noted in previous studies of patients with Cushing's syndrome. Such lessened responsiveness does not appear to be secondary to the hypercortisolism seen in these patients. Responses to insulin hypoglycemia in corticosteroid treated patients have not been cited

TABLE V

Plasma Corticosteroid Response (Mean Increment—μg/100 ml.)

	Insulin Hypoglycemia	Piromen	Vasopressin
	n	*n*	*n*
Normal	(104) 16.5	(95) 16.9	(178) 13.5
Cushing's			
Hyperplasia	(20) 2.3	(11) 10.4	(23) 21.6
Adenoma			(2)△ 2.5, 0
Normal			
(Steroid Rx)		(7)* 15.9	(7)* 12.0
		(10)°° 5.8	(31) 1.8

* 15–40mg. Pred.q.d. 1 week–2 months.

°° Dex. 1 mg. 11:00PM and 8:00AM prior to testing, adrenal responsiveness to ACTH not studied.

△ Responsive to ACTH.

in this table because of the variability of steroid dose and duration used in reported studies. It would appear however, that once adrenal responsiveness to ACTH returns in such patients, somewhat diminished, but not absent corticosteroid responses to hypoglycemia are present. The studies cited for Piromen® would also indicate that hypercortisolism was not a factor in the diminished responsiveness. In the ten instances where a decreased response was seen, prior ability of the adrenal to respond to ACTH was not ascertained (41).

Additional evidence that may be cited in support of altered central nervous system function in patients with Cushing's syndrome are the observations of the persistence of some of the endocrine abnormalities when patients are in clinical remission following radiotherapy. Radiotherapy presumably acts by decreasing either the amount of CRF and/or ACTH available to cause adrenal stimulation, thereby leading to evidence of decreased adrenal cortical activity. It would not be expected to affect alterations in neurotransmitter content or feedback sensitivity. Therefore in the treated inactive patient one would expect to see normal responsiveness to ACTH and metyrapone but persistence of abnormality in parameters involving the central nervous system—i.e., stress responses, circadian periodicity and dexamethasone suppressability. This is precisely the case, as seen in Table VI, and as we have also reported elsewhere (42).

Abnormalities that we and others have noted with regard to neurally mediated growth hormone responsiveness in patients with Cushing's syndrome also support a concept of primary CNS involvement, rather than the possibility that such abnormalities are merely secondary to increased levels of circulating corticosteroids. As seen in Table VI and VII, decreased growth hormone responsiveness to hypoglycemia, pitressin and Piromen® is observed in patients with active Cushing's syndrome. Such decreased responsiveness is still seen, though to a lesser degree, in treated patients with Cushing's syndrome associated with hyperplasia, and tends to be normal in treated and untreated patients with Cushing's syndrome secondary to adrenal adenoma, although as indicated in Table VII, there is insufficient data to be conclusive in this latter group. Fur-

TABLE VI*

Growth Hormone and Cortisol Responses to Various Stimuli in Cushing's Syndrome

Patient	Insulin Tolerance		Piromen		Pitressin		Metyrapone	Dexamethasone Suppression		Circadian Pattern
	Cortisol	Growth Hormone	Cortisol	Growth Hormone	Cortisol	Growth Hormone		2 mg.	8 mg.	Plasma 11-OHCS
1. Active	Absent	Absent	Present	Absent	Present	Absent	+	Absent	Present	Abnormal
2. Active	Absent	Absent	Absent	Absent	Present	Absent	+	Absent	Present	Abnormal
Remission	Present	Absent					+	Absent	Present	—
3. Active	Absent†	Absent	Absent	Absent	Present	Absent	±	Absent	Absent	Flat
4. Remission	Absent	Absent	Absent	Absent	Present	Absent	+	Present	Present	Flat
5. Remission	Present	Absent	Present	Absent	Present	Absent	±	?	Present	Flat
6. Remission	Absent	Absent	Present	Absent	Present	Absent	+	Absent	Present	Flat

* Reproduced with permission from Krieger, D. T., and Glick, S.: Am J Med 52: 25, 1972.

† This patient showed no response to ACTH administration. Column one indicates clinical status of Cushing's syndrome.

TABLE VII

Insulin Hypoglycemia Growth Hormone Responsiveness (Mean Increment mug/ml.)

	n	
Normal Subjects	(65)	30.8
Cushing's Syndrome		
Active		
Hyperplasia	(27)	9.7
Adenoma	(4)	32.0
		77.7
		3.0
		0.5
Inactive		
Hyperplasia		
Rx -Adrex	(11)	14.0
Rx -X-ray	(3)	13.2
Adenoma		14.8
		63.2
		28.5
Normal Subjects		
Steroid Rx		
a) high dose long term	(6)	6.0
b) 36 mg. long term	(5)	16.0
c) high dose acute	(5)	15.0

Summary of literature to date on growth hormone responsiveness to hypoglycemia in normal subjects and states of hyperadrenocorticism. (See text for discussion.)

thermore, as noted in the studies with normal subjects, the long-term administration of a dose of cortisone that is comparable with the adrenal secretory rate in many patients with Cushing's syndrome does not lead to as profound a suppression of growth hormone responsiveness as seen in patients with Cushing's syndrome.

We have also demonstrated (36) that in patients with Cushing's syndrome, whether active or inactive, there is absence of the normal nocturnal rise in plasma growth hormone levels, as well as a marked diminution in the percent of time spent in slow wave sleep. Again these findings cannot be ascribed to hypercortisolism per se, since they are not reproduced by nocturnal elevation of plasma corticosteroid levels (43).

Implications with regard to Possible Therapeutic Approaches

As noted in the section dealing with central nervous system regulation of pituitary trophic hormone release, evidence has been presented with regard to both growth hormone and ACTH of possible adrenergic and serotonergic mediation of their release in response to specific stimuli (i.e., stress, circadian periodicity). It may well be that if central nervous dysfunction is etiologic in Cushing's syndrome associated with bilateral adrenal hyperplasia, this may be a functional disturbance involving, as suggested above, either decreased ratios of neurotransmitter substances or decreased sensitivity of neurotransmitter to appropriate feedback. If this were so, then by varying amine concentrations in CNS areas believed to be involved in pituitary trophic hormone regulation, one might be able to bring about an amelioration of the endocrine abnormalities seen in this disease.

One such approach would be to attempt to increase brain serotonin levels, by the administration of its precursor l-5-hydroxytryptophan, a compound which can cross the blood-brain barrier, unlike serotonin, and obviates the rate-limiting step of hydroxylation of tryptophan. Since animal data indicates that serotonin causes hippocampal excitation (44) (this structure being inhibitory to pituitary adrenal function), and depression of amygdalar firing (45) (this structure being excitatory to pituitary adrenal function) such an increase in serotonin levels might reverse some of the endocrine disturbances seen in Cushing's syndrome.

Another approach, in view of the reports of Van Loon et al (46) that evidence of adrenal hypersecretion in the rat following administration of a methyltyrosine (which decreases CNS catecholamine levels), is attenuated by concomitant L-DOPA administration, (which increases such catecholamine levels), is that administration of L-DOPA could be utilized in treatment of Cushing's syndrome. Both of these approaches are currently under investigation.

At present, currently available modes of therapy of Cushing's syndrome are not completely successful. Pituitary irradiation alone (cobalt therapy-4500R) is associated with remission or improvement in approximately two-thirds of the cases so treated (11) (12). Total adrenalectomy, though effectively eliminating adrenal hypersecretion, is associated with a 10–15 percent incidence of development of pituitary tumors post-operatively, such tumors tending to be more extensive and invasive than the usual type of chromophobe adenoma (17). A more direct approach to treatment, based upon an understanding of the pathophysiology involved, would be most desirable.

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Studies on Blood Coagulation

II. Kinetic Study of the Interaction between Antihemophilic Globulin and Antithrombin III in Normal and Hemophilic Sera

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Abstract

The inhibition of thrombin (enzyme) by antithrombin III (inhibitor) in normal or in hemophilic sera is not of the competitive type. The affinity of the inhibitor for the enzyme was found to be the same with normal and with hemophilic sera. Hemophilic sera, as a rule, was found to contain a higher concentration ($9.25 \times 10^{-6}M$) of the inhibitor than normal sera ($1.67 \times 10^{-6}M$). On addition of AHG concentrate to hemophilic sera the concentration of inhibitor was decreased to $5 \times 10^{-6}M$. The affinity of the enzyme for the inhibitor was found to be practically the same as that for the substrate (fibrinogen).

The current status of knowledge of antithrombin has been reviewed by Monkhouse (1).

In a previous paper (2) we showed that antihemophilic globulin (AHG) concentrate, added either to normal or hemophilic sera, lowered the antithrombin activity. Addition of AHG concentrate to serum caused neither proteolysis nor activation of any proteolytic system, and the decrease in antithrombin activity on addition of AHG concentrate to serum therefore could not be attributed to proteolytic destruction of the inhibitor. Since the assay measurements of antithrombin III were expressed in terms of activity rather than concentration, one cannot ascertain whether the decrease in antithrombin level was due either to a true decrease in concentration of the inhibitor or a conformational change of the molecule.

Kinetic analyses presented here were performed to obtain information on the reaction between AHG concentrate and antithrombin III in normal and in hemophilic sera. Serum was used as the source of antithrombin III. Adopting the approach of Taylor et al (3), we considered the inhibitior to be a globulin with a molecular weight of 300,000. By application of kinetic analysis we obtained an estimate of the concentration of the inhibitor.

Materials and Methods

Biological Reagents

Thrombin (enzyme). Parke-Davis Topical Thrombin (desiccated, 1000 National Units), dissolved in sterile isotonic saline.

Fibrinogen (substrate). Barium sulfate-treated normal plasma, prepared ac-

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cording to the method of Brown et al (4). Various dilutions were made with isotonic saline.

Serum (inhibitor). Human blood, collected from an antecubital vein, was permitted to clot and stand at room temperature for several hours. It was kept in the refrigerator over night and centrifuged; the serum was removed and stored at 5°C. This serum, without other treatment, was the source of the inhibitor (antithrombin III).

Antihemophilic globulin (AHG or Factor VIII) concentrate. Desiccated concentrate was provided by Connaught Laboratories, University of Toronto, Toronto, Ont.

Assay System

Two systems were studied, namely, thrombin-fibrinogen-inhibitor with and without added AHG concentrate.

The procedure for assay of inhibitor (antithrombin III) activity has been described (2).

Methods of Estimating Concentrations

1. *Fibrinogen.* The concentration of fibrinogen in $BaSO_4$-treated plasma, determined according to the method of Heikinheimo (5), was 340 mg/100 ml. Assuming 300,000 molecular weight (6), molar concentration would be 0.88×10^{-5}. Desired concentrations were prepared by dilution with sterile isotonic saline.

2. *Inhibitor.* The procedure of Taylor et al (7) was followed for study of the kinetics of the thrombin-inhibitor system. A concentration of 0.05 g/100 ml, and a molecular weight of 300,000 (mean molecular weight of α-globulins) were assigned to the inhibitor. Inhibitor concentration was calculated from a Dixon expansion, as indicated later.

Calculation of Affinities (8)

1. *Enzyme-substrate.* Affinity of enzyme for substrate, $1/K_m$, was calculated as follows:

If K_m represents the equilibrium constant

$$\frac{1}{K_m} = \frac{v}{[S](V_m - v)} \quad \ldots\ldots (1)$$

where

K_m = equilibrium constant of the uninhibited system,
v = velocity at a given substrate concentration,
v = 1/clotting time (sec)
V_m = maximum velocity of the uninhibited system,
$[S]$ = substrate concentration in moles per liter.

From the Lineweaver-Burk plot and the equation (1) above, the affinity of thrombin for fibrinogen can be estimated.

2. *Enzyme-inhibitor.* Affinity of inhibitor for enzyme was calculated as follows

$$\frac{1}{K_i} = \frac{(V_m/V_p) - 1}{[I]} \qquad (2)$$

where

K_i = inhibitor constant,
V_m = maximum velocity of the uninhibited system,
V_P = maximum velocity of the inhibited system,
$[I]$ = inhibitor concentration in moles per liter.

Results

The thrombin-catalyzed conversion of fibrinogen, as a function of substrate concentration, [S], is indicated in Fig. 1. The initial velocity was linear up to a substrate concentration of $0.88 \times 10^{-5}M$, thus indicating a first order reaction.

A Lineweaver-Burk plot of the results, obtained with and without inhibitor, is shown in Fig. 2. The maximum velocity for uninhibited (line A) and inhibited systems (lines B and B^1) are different, while the intercept of the abscissa is independent of the inhibitor concentration. The intercept of line C (hemophilic serum) was the same as that of line B (normal serum). The addition of AHG to hemophilic serum did not change the intercept of line C^1 on the $1/_{[S]}$-axis.

The Dixon expansion is shown in Fig. 3 in which the reciprocal of the velocity, as a function of the inhibitor concentration, is plotted for various

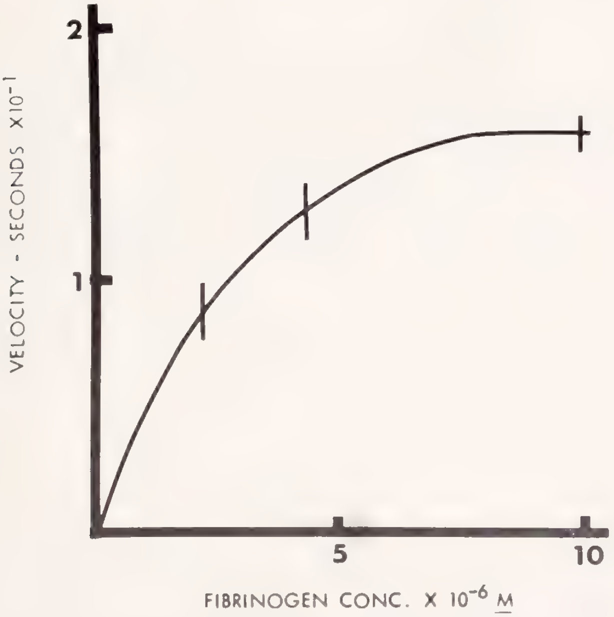

Fig. 1. Velocity of the thrombin-fibrinogen reaction as a function of fibrinogen concentration. Each plot is the average of 3 measurements. Enzyme (thrombin) concentration 10 N.U.

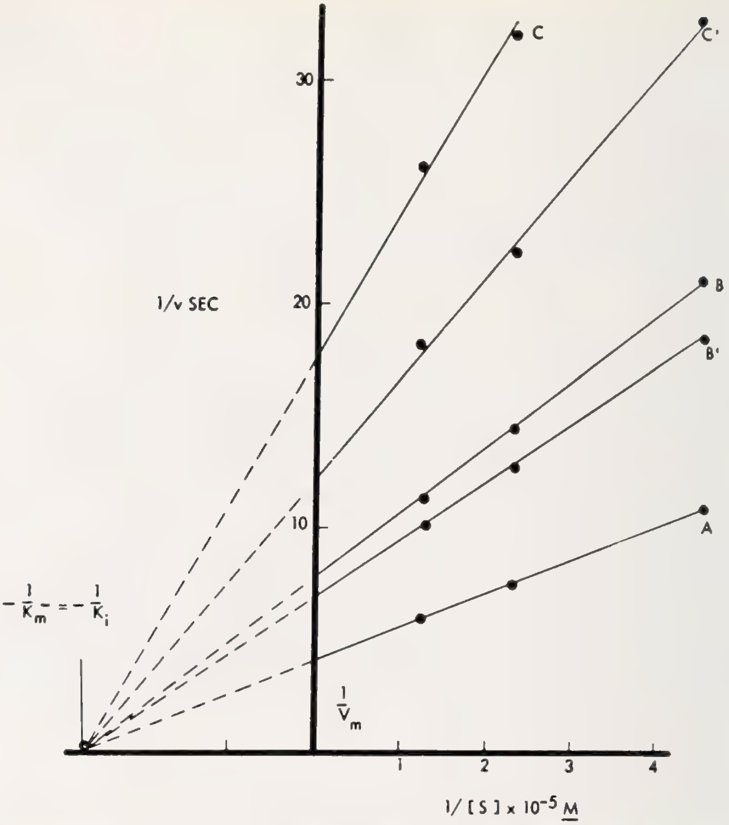

FIG. 2. Lineweaver-Burk plot of thrombin-fibrinogen and thrombin-fibrinogen-inhibitor systems. Plots of the reciprocal of velocity as a function of the reciprocal of substrate concentration in absence and present of various concentrations of inhibitor. A: Thrombin fibrinogen system (E + S). [E] = 10 N. Units. B: Thrombin/fibrinogen/normal serum (E + S + I). Concentration of inhibitor, 1.67×10^{-6} *M*. B′: Same system as B. Concentration of inhibitor, 0.83×10^{-6} *M*. C: Thrombin/fibrinogen/hemophilic serum. Concentration of inhibitor in serum unknown. C′: Thrombin/fibrinogen/hemophilic serum which contains 4.0 mg AHG concentrate/ml. All points represent the mean of 6 measurements.

substrate concentrations. The expansion enables one to estimate the concentration of the inhibitor. The concentration of antithrombin III in normal serum was found to be $1.67 \times 10^{-6}M$ and in the hemophilic serum, $9.25 \times 10^{-6}M$. On addition of AHG concentrate, the concentration of inhibitor in hemophilic serum was decreased to $5 \times 10^{-6}M$.

Discussion

In agreement with the observation of Monkhouse (1), Astrup and Darling (9, 10), and von Kaulla and von Kaulla (11), we found a first order reaction between thrombin and antithrombin.

The plot, in Fig. 2, of the reciprocal of velocity as a function of the reciprocal of substrate concentration, is linear for the various concentrations of thrombin inhibitor in normal and hemophilic sera.

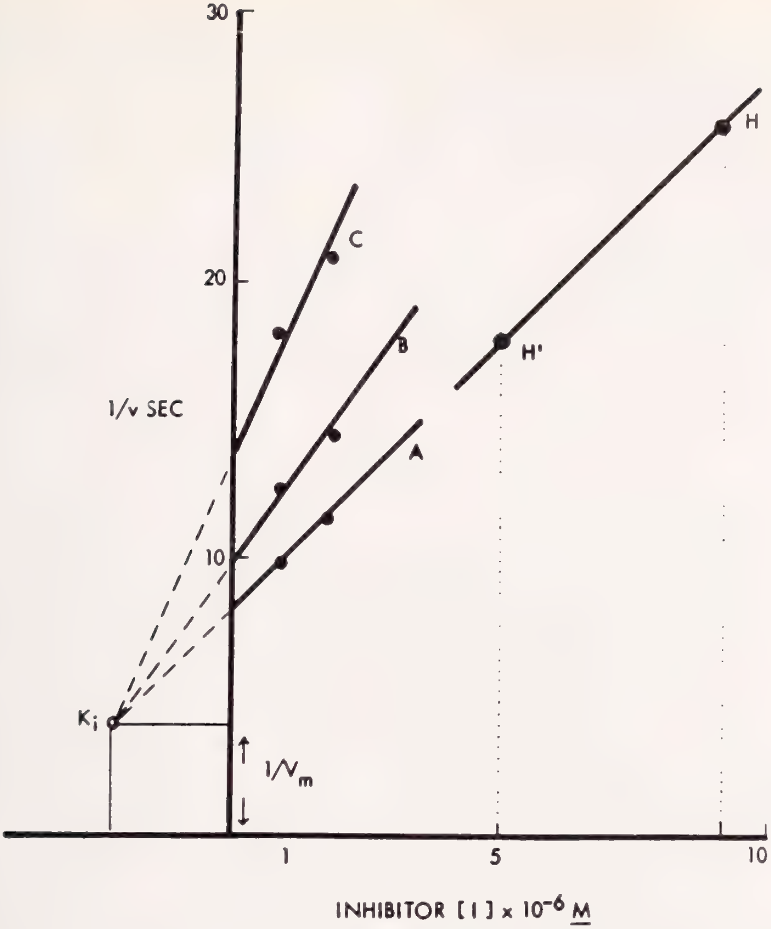

FIG. 3. Dixon expansion for thrombin-fibrinogen-inhibitor system. Plots of the reciprocal of the velocity as a function of inhibitor concentration for various concentrations of substrate. A: Substrate (fibrinogen) concentration, 0.88 × 10^{-5} *M*. B: Substrate concentration, 0.44 × 10^{-5} *M*. C: Substrate concentration, 0.22 × 10^{-5} *M*. H: Hemophilic serum used as inhibitor source, with substrate concentration of 0.88 × 10^{-5} *M*. H′: Same systems as H, except that the hemophilic serum was preincubated with concentrate (4.0 mg/ml) for 15 minutes, at 37°C. The enzyme concentration in all cases was 10 N.U. of thrombin in 0.05 ml of saline. All points are the average of 6 measurements.

As the maximum velocity of the uninhibited system differs from that of the inhibited system (Fig. 2) while the intercept on the $1/_{[S]}$-axis is independent of the inhibitor concentration for both normal and hemophilic specimens, the analysis indicates that inhibition of thrombin by antithrombin III is not competitive in character. It is evident, further, that specimens of hemophilic serum differed only in respect to the concentration of inhibitor, and that the effect of adding AHG preparation was merely that of dilution of inhibitor. The findings suggest also that the antithrombins both of normal and hemophilic sera behave similarly toward thrombin in that neither attaches to the active site of the enzyme.

The Dixon expansion in Fig. 3 shows that the concentration of inhibitor in hemophilic serum was more than five times that of normal serum. On addition of AHG the inhibitor concentration was decreased from $9.25 \times 10^{-6}M$ to $5.0 \times 10^{-6}M$. The latter value is still about 3 times higher than that of normal serum inhibitor. The linear relationship obtained in the Dixon expansion signifies that the inhibition is of the noncompetitive type and that it is not an allosteric phenomenon.

The affinity of the inhibitor for the enzymes was the same for both normal and hemophilic sera, thus suggesting that both inhibitors may be identical.

The results indicate also that increased antithrombin activity in hemophilic sera (2) is attributable to an increase in the concentration of inhibitor (ii), and that decrease in activity on addition of AHG concentrate is attributable to inactivation of antithrombin III.

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Combination Chemotherapy for Advanced Mammary Carcinoma: A Twelve-Year Experience

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Approximately 100,000 women are suffering from metastatic or incurable breast cancer in the United States today. Most of these patients now receive exposure to one and often several forms of hormonal and ablative therapy during an average two-year course of metastatic disease before being considered for chemotherapy in either the "late phase" of dissemination or in a preterminal state. The limitations of hormonal-ablation therapy have been well established. At least 50 000 patients are currently suffering from recurrent or hormonally-resistant symptomatic metastases which should be treated with chemotherapy. Another 25 000 harbor occult Stage II B incurable metastases. These 75,000 patients represent the largest number of adults with advanced cancer potentially able to be influenced by chemotherapy, exceeding the number of cases of lymphoma, leukemia, or recurrent gastrointestinal neoplasm.

The experimental rationale for the use of anticancer drug combinations to achieve increased tumor inhibition and prolonged host survival has been thoroughly established and reviewed (1–3), as well as demonstrated clinically (4–13). Drugs acting to inhibit their growth by different biochemical mechanisms can be expected to show synergistic effects provided drug toxicity is not unduly enhanced and can be ameliorated by anabolic hematostimulants. The goal of the experimental and clinical chemotherapist is to delay the ultimate development of tumor resistance and to determine what are the optimum timing dosage schedules for chemotherapy. Premature therapy and overdosage are as unsuitable as homeopathic underdosage or futile single-drug therapy.

A rational methodical approach to the chemotherapy of incurable breast cancer still eludes us more than two decades after the first demonstrations that breast cancer was relatively sensitive to the inhibiting action of both alkylating agents and antimetabolites. The confusing state of breast cancer chemotherapy stems in part from the varied unpredictable growth characteristics of human breast cancer when viewed in broad heterogeneous groups of patients. Differences in previous surgical, ablative, radiation and hormonal therapy, and particularly in the recurrence-free interval (14) also account for many difficulties in evaluating results of chemotherapy, especially whenever the latter is offered as a late, erratic one-drug effort in preterminal patients (15). More than any other common neoplasm, breast cancer tends to grow in clinically recognizable discrete metastatic patterns in predominant major organ sites. The separation of patients into well-defined, small cohorts based upon the site of the predominant organ metastatic patterns has revealed data indicating that some agents seem to exert a preferential effect on certain organ metastatic sites, formerly associated with short survival (Table I).

Our published experiences during the past decade (8, 9) and the recent confirmatory observations of Cooper (11) have established that multiple, simultaneous, two, three or four drug cytotoxic therapy should be expected to in-

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TABLE I

Estimated expected survival of patients according to predominant clinical pattern prior to combination chemotherapy era

Site	1 Year Survival	2 Year Survival
Liver	18%	5-7%
CNS (Brain)	15%	4-5%
Pulmonary Lymphangitic	15%	2-4%
Inflammatory Carcinoma	20%	8-10%
Pleura and/or Lung	25%	10-15%
Osseous		
Androgens (<10 yrs. post menopausal	35%	7-15%
Estrogens (>10 yrs. post menopausal)	63%	7-15%
Soft Part		
Androgens (<10 yrs. post menopausal)	55%	25%
Estrogens (>10 yrs. post menopausal)	85%	40%

* From various authors, including Cutler, Ariel, Escher, Greenspan, etc.

duce a substantial "tumor kill" manifested clinically by significant objective regression in from 60 to 85 percent of unselected heterogeneous metastatic patients with or without previous hormonal ablative response. Only 15 percent of patients should be expected to show no response to multiple combination chemotherapy aided by adrenal steroids and androgens (9, 11). These observations indicate that the relation of hormone-ablative therapy to chemotherapy must now be clearly reassessed in the light of the frequent tumor regressions obtainable with combination chemotherapy.

The manner of obtaining the optimum "tumor kill" and maintaining the optimum duration of control with least toxicity with various combinations of the four major agents (Thio-TEPA, Methotrexate, Fluorouracil and Cytoxan) has not been delineated. All breast cancer chemotherapy studies have thus far been retrospective without broadly directed simultaneous single drug comparative studies. Review of the clinical literature on mammary cancer chemotherapy indicates that single drug therapy (5-FU, Cytoxan, Thio-TEPA or Methotrexate and Vincristine) for varied types of advanced mammary carcinomas should be expected (17–19) to yield short term (3-4 months) regression rates of about 25 to 35 percent. Higher response rates from primary single drug therapy usually reflect less rigid criteria for response, undue enthusiasm in reporting results in early "fresh" metastatic cases or a willingness to cope with unusual toxicity. The regression control from a single cytotoxic agent such as Chlorambucil or 5-FU seems to be qualitatively improved with steroid therapy (20, 21) at least in the short run.

The simultaneous use (8) of an alkylating agent and an antimetabolite (Thio-TEPA and Methotrexate) (Combination A-Fig. 1) was adopted by us routinely in 1959. In a series of sixty hormone-resistant breast cancer patients treated between 1959 and 1962 we obtained 60 percent regression rates. This compared with a 25 to 35 percent regression rate usually expected from either drug alone. Responses at this 60 percent rate occurred without adrenal steroid therapy in patients with metastases to the skin, subcutaneous tissue, chest wall, lung, and central nervous system, but not among two important metastatic sites, i.e., those cohorts presenting either with predominant massive hepatomegaly or predominantly diffuse osseous metastases. These latter important groups showed a disproportionately low response rate of only 15 to 20 percent after Thio-TEPA plus Methotrexate therapy. Because of this lack of clinical synergism between Thio-TEPA and Methotrexate in the group with predominant liver metastases, 5-Fluorouracil (Combination C$_1$, Fig. 1) was routinely added after 1962 to form a triple drug regimen for all patients presenting with major hepatic metastasis. This 5-Fluorouracil triple drug regimen, with toxicity significantly reduced by Prednisone and Testosterone, resulted in marked hepatic regression (Fig. 2) in more than 80 percent of patients (Table II) presenting for treatment of massive hepatomegaly (22). The significance of this unexpectedly high regression rate, indicating clinical synergism, was amplified by Dao and Grinberg's report (23) that single drug therapy with 5-Fluorouracil alone resulted in only 35 percent regressions among similar cases of massive hepatomegaly. Worthwhile clinical remissions of more than three months' duration (22) were achieved in 75 percent of these preterminal cases. The relatively selective action of 5-FU on liver metastases appeared to be related to the increased 5-FU concentration in the liver, biliary tree, and upper GI tract seen in experimental animals (24).

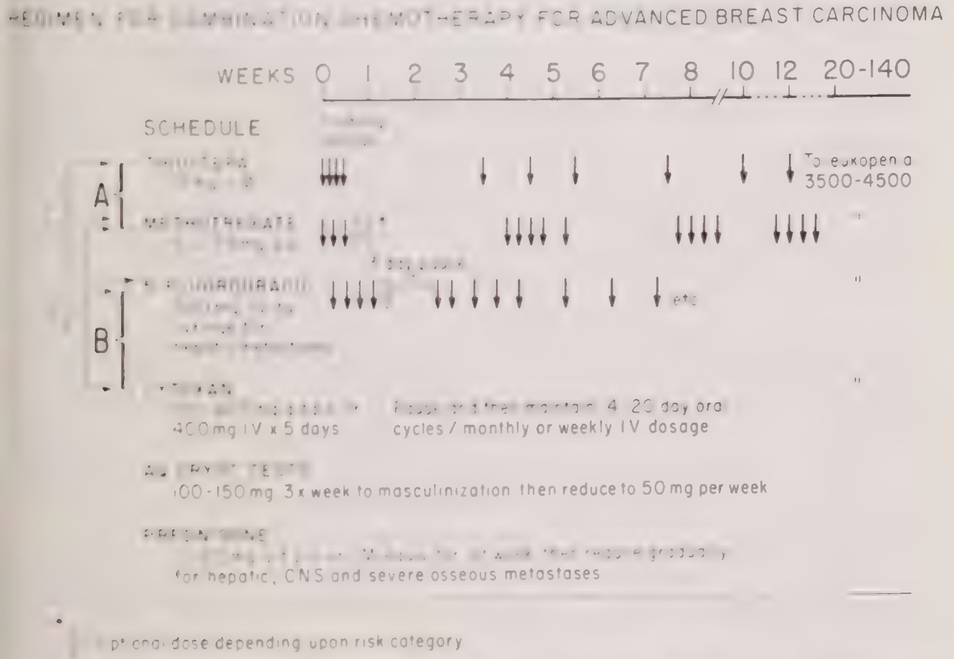
FOR ADVANCED BREAST CARCINOMA
WEEKS 0 1 2 3 4 5 6 7 8 10 12 20-140
SCHEDULE
A
B
To leukopenia 3500-4500
etc
400mg IV x 5 days
cycles / monthly or weekly IV dosage
100-150 mg 3x week to masculinization then reduce to 50 mg per week
for hepatic, CNS and severe osseous metastases
dose depending upon risk category

FIG. 1. Four major combinations (A, B, C$_1$, C$_2$) employed with priming dosage, cycles and/or maintenance therapy indicated.

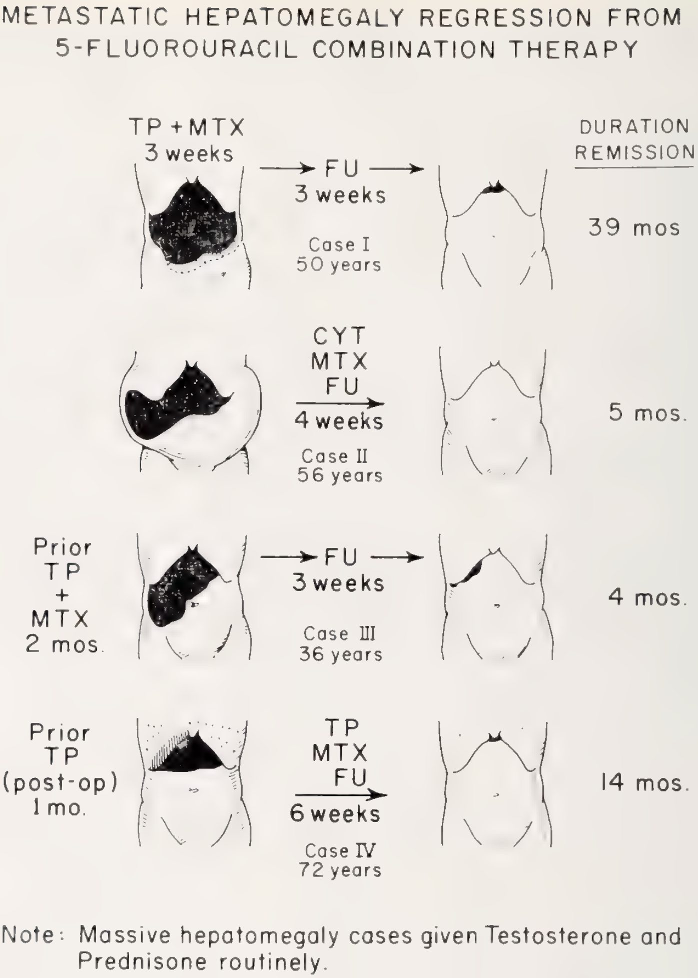
METASTATIC HEPATOMEGALY REGRESSION FROM 5-FLUOROURACIL COMBINATION THERAPY
TP + MTX 3 weeks
FU 3 weeks
Case I 50 years
DURATION REMISSION
39 mos
CYT MTX FU 4 weeks
Case II 56 years
5 mos.
Prior TP + MTX 2 mos.
FU 3 weeks
Case III 36 years
4 mos.
Prior TP (post-op) 1 mo.
TP MTX FU 6 weeks
Case IV 72 years
14 mos.
Note: Massive hepatomegaly cases given Testosterone and Prednisone routinely.

FIG. 2. The rapid regression of hepatomegaly achievable by triple 5-FU therapy.

TABLE II

Increased one-year survival obtained in life-threatening metastases after chemotherapy (Combination A)

	Regression > 3 Mos.	Survival > 1 Year
Inflammatory Cancer	15/16	12/16
Pulmonary Lymphangitic	8/14	7/14
Massive Hepatomegaly		
Without F.U.	1/8	1/8
With F.U. (Triple Therapy)	15/20	9/20
Cerebral Metastases		
No Radiotherapy	8/15	4/15
With Radiotherapy	9/10	7/10

The results of cyclophosphamide therapy for diffuse bone metastases also suggest (9) that the selection of an optimally effective agent may depend on the site of predominant organ metastases. Thus, patient cohorts with diffuse osseous metastases showed enhanced and sustained control when Cytoxan was initiated and maintained two months after ineffective but intensive courses of Thio-TEPA plus Methotrexate. This secondary response indicating lack of cross-resistance of the tumor to Cytoxan appeared analogous to Cytoxan-induced regressions reported (25) in angiosarcomas likewise resistant to Thio-TEPA and Methotrexate. The significantly better effect of Cytoxan alone on bone metastases compared to 5-Fluorouracil alone, was recently reported by Nemoto and Dao (26) in osseous metastases recurring postadrenalectomy. This study confirmed our clinical impression that the atypical alkylating agent, Cytoxan, should be considered as a preferred single drug if one drug only is employed for treatment of diffuse osseous metastases.

The prompt regressive effect of toxic oral courses of Methotrexate initially observed by Wright (28) on 32 percent of skin and subcutaneous metastases, was extended to a 60 percent rate by simultaneous (9) additional Thio-TEPA to Methotrexate. Repeated cycles of Methotrexate every four to eight weeks accompanied by Thio-TEPA maintenance therapy appeared warranted when any recognizable degree of regression occurred during the first course pushed to oral mucosal ulceration. Women with visible growing subcutaneous nodular or ulcera-nodular chest wall metastases willingly tolerated moderated Methotrexate toxicity repeatedly if they witnessed a definite regression of metastases seven to 14 days after onset of the antimetabolite therapy. However, these courses of Methotrexate could not be safely given unless therapy was individually titrated (Fig. 3) by an aggregate (per week) dosage template (6) differentiating poor risk from good risk patients. These important dosage stoichiometrics based on medical risk category have been generally ignored by most clinicians until recently. The numerous clinical features of the poor risk patient include not only marginal renal function but other diverse important clinical manifestations (Table III). The rapid approach of the Methotrexate toxic-therapeutic phase, only 7 to 10 days after onset of chemotherapy, provides a reliable and convenient guide to management since metastases which show no regression whatsoever in this short time can be treated soon thereafter with other agents.

The striking inhibitory effect of Methotrexate and Thio-TEPA on inflammatory carcinoma (Table II) was demonstrated by rapid, substantial regression in fifteen of a group of sixteen patients (27). Comparable studies of single drugs are still not available to establish whether the repeated cycles of Methotrexate alone are the major factor responsible for obtaining more than one year of control in most fresh cases of inflammatory breast cancer (Table II) with Thio-TEPA and Methotrexate. The 75 percent one-year survival in patients with inflammatory cancer certainly indicates that combination chemotherapy does not lower host resistance or tumor immunity in the dosage cycles and schedules employed.

The disappearance of steroid-resistant central nervous system deficits from

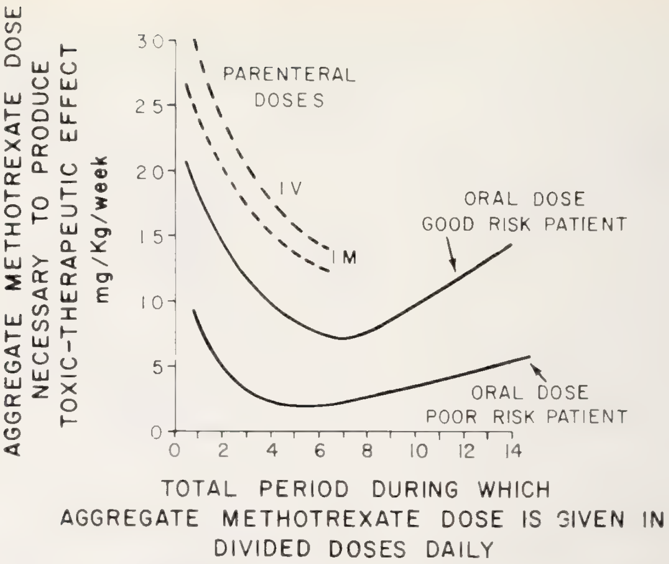

Fig. 3. Dose Template indicating marked differences in aggregate Methotrexate dosage tolerated by good risk compared to poor risk patient. The more rapidly developing toxicity and the slower rate of recovery of the poor risk patient can be inferred by the sharp drop in cumulated drug tolerance during the toxic induction and the tardy increased tolerance during the recovery phase.

TABLE III

Clinical features of poor risk candidate for combination chemotherapy

Extensive x-ray therapy to bones
Diffuse osseous metastases
Impaired renal function
Massive metastic hepatomegaly
Marked anemia, hypoproteinemia
Protracted vomiting, diarrhea
Severe cachexia or depression
Prolonged therapy:
  I.V. fluids, Antibiotics,
  Steroids, Diuretics
Colostomy, nephrostomy, etc.
Open postoperative infected (gram negative) channels
Old age over 65

cerebral metastases within a few days after acute systemic Methotrexate toxicity (without any intrathecal Methotrexate in our early series) was observed in 60 percent of more than 25 patients suffering principally from progressive central nervous system metastases (27). Apparently, prompt regression of intracranial metastases was accompanied in many patients by a simultaneously rapid regression of pulmonary metastases, usually as the Methotrexate stomatitis was subsiding. These observations have since encouraged the emergency use of systemic Methotrexate (as well as intrathecal Methotrexate), accompanied by an alkylating agent (Thio-TEPA or Cytoxan) followed within ten to 21 days after onset of the chemotherapy by broadside, usually non-localized supervoltage radiotherapy to the skull. It is noteworthy that fatal metastatic recurrence developed more often in the lungs or liver than in the cranium more than a year after the chemotherapy plus radiotherapy attack (24) on central nervous system metastases compared to the two to fourteen months for those on combination chemotherapy alone (Table II). Comparative prospective studies are thus far lacking to provide statistical support for this clinical impression of the potent suppressive effect of Methotrexate on cerebral metastases.

Lymphangitic carcinomatosis of the lungs, a heretofore irreversible and rapidly fatal metastatic syndrome, has also shown objective regression after combination chemotherapy in half (Table II) of a group of 14 patients treated for acute respiratory insufficiency. Many responders have survived for more than one year and have been maintained, in a few instances, for as long as three years. The more recent rapid lymphangitic infiltrations appear to respond more completely than those present for several months or more prior to therapy.

Table IV summarizes the stepwise increase in the rate of tumor regression obtainable by the addition of multiple drugs in large heterogeneous series of advanced metastases cases. The 25% to 40% rate obtained by most observers from single drugs contrasts with a 60% regression rate after two simultaneous drugs (Thio-TEPA plus Methotrexate), and a 75 to 80 percent regression rate after three drug therapy. The striking potency of four drug therapy, recently reported in a heterogeneous series by Cooper (11), is based on major regression induced in more than 80 percent of 60 diverse cases of hormone-resistant metastases treated with simultaneous Methotrexate, Cytoxan, 5-Fluorouracil, and Vincristine, all supported by high initial dosage of adrenal steroids. The clinical merit of the addition of Cooper's fourth cytotoxic agent (Vincristine) remains to be demonstrated since it is associated with special

TABLE IV

Increased regression rates reported after combination chemotherapy

Expected Regression Rates	
Single Cytotoxic Agent	
5-FU	30-40%
Thio-TEPA	35-40%
Cytoxan	30-40%
Methotrexate	32%
Vincristine	26%
Double Combination	
Thio-TEPA and Methotrexate	60%
5-FU and Prednisone	60%
Triple Combination	
5-FU, Thio-TEPA, and Methotrexate	80%
Quadruple Combination	
5-FU, Methotrexate, Vincristine and Cytoxan	80-85%

technical disadvantages in women with compromised upper extremity veins. Vincristine appears less effective alone (26 percent) than the four major cytotoxic agents (19). The obvious increase in regression rate by the addition of the second, third and fourth agents in combination parallels a progressive clinically recognizable increase in "tumor cell kill". It is doubtful whether the regression rate with five or more simultaneous cytotoxic agents could go much higher than the 80 to 85 percent reported with four drugs, since a hard core of 10 to 15 percent of uncontrollable drug-resistant cases of mammary cancer continues to be observed despite all attempts at the most vigorous combinations and sequences of standard or new investigative agents.

Controlled single drug sequence studies comparing the four agents, i.e., Thio-TEPA, Methotrexate, Cytoxan and 5-Fluorouracil, have not yet been reported. However, the lack of cross-resistance observed between these four major drugs against diverse animal tumors has been confirmed clinically in many patients treated with the two sets of double combinations and with some single sequences. The patient is her own control in this situation. Half of those patients who develop resistant or recurrent metastases or a new contralateral independent primary tumor while on Thio-TEPA and Methotrexate therapy have subsequently shown substantial objective regressions with Cytoxan and or 5-Fluorouracil therapy (Combination B).

The clinical management, toxicity, and psychological factors with Thio-TEPA and Methotrexate as the initial combination (Combination A) seemed more predictable and less complicated than after Cytoxan plus 5-Fluorouracil therapy (Combination B). We have therefore reserved Cytoxan plus 5-Fluorouracil as the "secondary double combination" for chemotherapy-resistance when the initial preferred combination, Thio-TEPA and Methotrexate, has not controlled the common metastatic sites of skin, chest wall, lymph nodes, soft tissue, lung, and pleura.

The sequence of two double combinations (Fig. 1) routinely applied to these relatively non-dire metastatic sites resulted in a primary remission (Combination A) of seven months' median duration for the 60 percent of responses in these common metastatic sites. Secondary remission, usually less complete, was sustained for another four to six months in about one-half of those completing the second double combination (Combination B). It is noteworthy that Cooper's median remission (11) duration was only ten months after Methotrexate, Cytoxan, 5-Fluorouracil, and Vincristine as a primary four drug chemotherapy combination (with substantial doses of adrenal steroids and without Thio-TEPA). His remission duration appears to be 2 to 3 months better than the 7-month median remission duration obtained by us after Thio-TEPA plus Methotrexate. However, since almost half of our "secondary" responders to Cytoxan and 5-FU survived an additional period of four to six months, the median remission differences between the two-followed-by-two drug regimen, compared to the simultaneous four drug regimen seem negligible and may favor the former. Moreover, those who showed good to excellent regression (greater than 80 percent "tumor kill") from the first two-drug combination with more than a seven month median remission duration usually obtained an extra survival, often six to nine months longer, with the second two-drug (5-Fluorouracil and Cytoxan) combination. The burden and hazards of carrying on the simultaneous four drug regimen of Cooper are substantial. The major question thus remains whether the four best-studied drugs (Thio-TEPA, Methotrexate, Cytoxan and 5-Fluorouracil) can produce longer remission duration and better clinical control by a bold simultaneous four drug program or by two sets of two drugs, each employed in succession.

No responses to Chlorambucil, Actinomycin-D, or Vinca alkaloids have been observed in a small number of cases treated after failure of the four major drugs. If the optimum approach is indeed to "throw our bolt" all at once in an attempt to obtain initial maximal tumor kill, then there is no promising agent to turn to for late relapse. These questions regarding combination chemotherapy will remain unanswered until long range prospective studies are undertaken over many years on a collaborative, multi-institutional basis. Simpler, more direct questions regarding single agents also remain unanswered, viz, whether a single standard radiomimetic alkylating agent such as Thio-TEPA or Chlorambucil is futile for a patient with known metastases recurrent in previously radiation-treated areas. We do not have any controlled data on which is the single preferred agent, or preferred sequence of single agents for the patient with relatively slow-growing metastases, despite the large clinical literature on mammary cancer chemotherapy.

Although there are large gaps in our knowledge of these agents, it is obvious the chemotherapy in metastatic breast cancer is no longer an academic matter. Patients and pragmatic clinicians do not and should not wish to delay the use of potentially effective agents simply because extensive scientific controlled studies are lacking. The relationship of sequential and combination chemotherapy to hormone-ablative therapy will also remain obscure pending at least five to ten years of careful collaborative national studies yet to be organized. Lacking much basic clinical data, we nevertheless offer a tentative useful scheme (Fig. 4) for a chemotherapeutic approach to the individual with metastatic mammary cancer based on our more than ten years' experience with the four major cytotoxic agents.

The essential clinical evaluation depends on assessment of the age and recurrence-free interval, if any, of the patient, and the location, growth characteristics, and number of metastatic organ sites, balanced by the medical risk category of the patient for chemotherapy. Reliance on one drug alone appears no longer tenable except in slow-growing, non-life-threatening metastases after a long recurrence-free interval. The older patient with slow-growing metastases may well be allowed to undergo hormonal or hormonal-ablative therapy for the six to twelve weeks necessary to evaluate an endocrine approach, and then to follow this with single drug therapy. However, the woman with rapidly growing, life-threatening metastases, especially if below the age of 60 with a short recurrence-free interval, warrants prompt use of combination and/or sequential chemotherapy (Table V). The more rapidly growing the metastases, the less

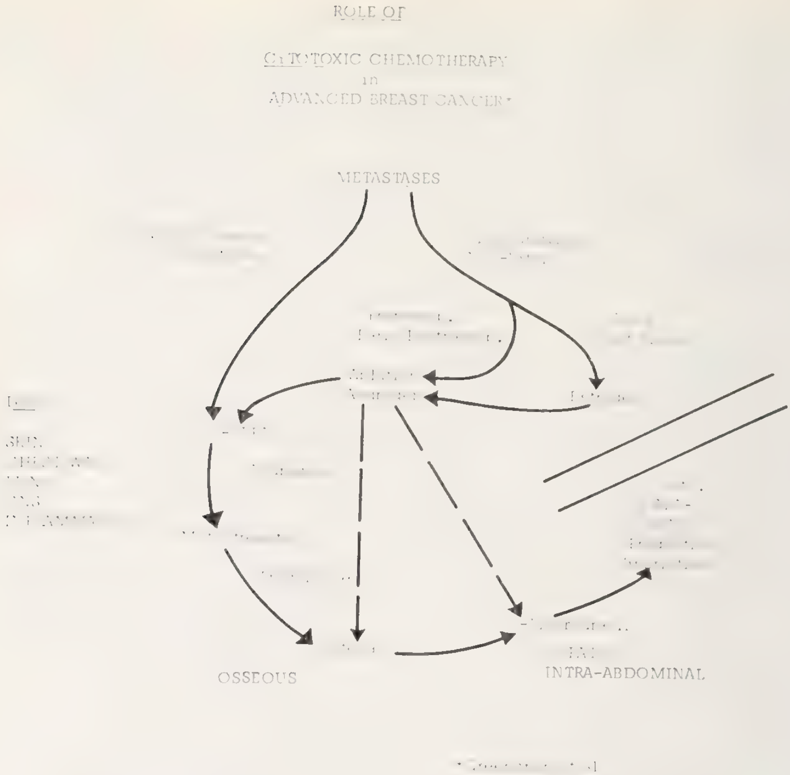
ROLE OF
CYTOTOXIC CHEMOTHERAPY
in
ADVANCED BREAST CANCER*
METASTASES
SKIN
OSSEOUS
INTRA-ABDOMINAL

Fig. 4. Schematic chemotherapeutic approach to breast cancer.

TABLE V

Factors influencing choice of single or combination chemotherapy

Single vs Combination Chemotherapy	
Single	Combination
Factors	
Nonlife threatening	Life-threatening
One major metastatic site	Two or more metastatic sites
Slow-growing	Rapidly growing
Long recurrence-free interval (>2 years)	Short recurrence-free interval (<2 years)
Older patient	Young patient
Poor medical risk	Good medical risk
Nonfactors	
Previous Endocrine Dependence	
Menopausal Status	

likely will single drugs be sufficient to induce regression especially in women under 45 years of age, and especially if two or more sites of dissemination are apparent. Although Cytoxan alone appears to be sufficient as a first-drug single alkylating agent for slow-growing multifocal bone metastases without significant extraosseous metastases, 5-FU alone is certainly insufficient for major hepatic metastases. Substantial diffuse infiltration in such vital organ sites as lung or liver warrants double or triple therapy respectively, with significant adrenal steroid support. Massive hepatic "dire" metastases should be treated with 5-Fluorouracil plus Thio-TEPA and Methotrexate as an urgent initial triple combination. Prompt treatment of inflammatory carcinoma and emergency treatment of brain metastases with combination therapy is essential if optimum regression and reduced morbidity is to be obtained. Critically ill patients with seven to 14 days of life expectancy after a one-drug failure probably warrant triple chemotherapy. The routine use of Testosterone as an anabolic hematostimulant in all cases of mammary carcinoma receiving chemotherapy is advocated, together with adrenal steroids for life-threatening brain or visceral infiltrations.

The abrupt, often dramatic regression and the subsequent control of metastatic disease after combination chemotherapy for six to 18 months should not obscure the dismal fact that long-term control for more than two years after onset of chemotherapy was achievable in less than 15 percent of our large series of patients coming for treatment of recurrent mammary carcinoma. Although the initial regression rate for the first year on combination chemotherapy is much higher than after hormonal-ablative therapy the residual number of chemotherapy-controlled cases at the end of two years is probably no greater than after hormonal ablative therapy. Five year survivorships after onset of chemotherapy still number less than 3 percent despite all efforts in our series of patients.

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Management of Ovarian Carcinoma: A Review of 14 Years' Experience at Beth Israel Hospital

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Systemic chemotherapy in the treatment of disseminated ovarian carcinoma has been in use at the Beth Israel Medical Center since 1958. Until that time, the usual approach to this disease comprised surgery with the addition of ortho-voltage or supervoltage radiation therapy. The survival rate was poor although some palliation and occasional long-term survival occurred. A more effective approach to therapy was sought. With the availability of potent chemotherapeutic agents, an investigational approach to the treatment of ovarian carcinoma was developed using thio-tepa (triethylene thiophosphoramide) in conjunction with surgery. Initially, the use of chemotherapy was considered experimental, and patients or physicians might choose to employ the new drug. With increasing experience, the staff has elected this course of treatment almost without exception. Our experience and conclusions with the use of thio-tepa chemotherapy following surgery for the treatment of ovarian carcinoma are presented.

Because symptoms leading to medical attention appear late in the natural history of ovarian carcinoma, and techniques for early diagnosis are limited (1, 2), the majority of patients are seen in the late stages (3). Abdominal distention, self-detection of tumor masses, and the frequent vague abdominal and gastrointestinal complaints usually become evident long after the possibility of complete surgical excision has been lost. Routine examination or surgery for other indications may lead to the removal of a Stage I tumor, but the majority of patients seen with ovarian carcinoma are in Stages II, III, or IV, when large abdominal masses, ascites, and cul-de-sac nodularity signal a late stage and poor prognosis. Initial surgery is often limited to an intraperitoneal biopsy of omental or peritoneal metastases, although hysterectomy with removal of both adnexa, if possible, is generally but not universally advocated. In some centers, omentectomy is added for its possible beneficial effect on ascites. A super-radical surgical approach, including exenteration, has not proven worthwhile for ovarian carcinoma (4).

Advocates of radiation or chemotherapy will differ in the post-operative management of disseminated ovarian carcinoma. For Stage II disease, external pelvic radiation may constitute sufficient treatment, while for Stage III disease, whole-abdomen radiation is necessary (5). Variations in technique including strip therapy are available, but radical radiation therapy is not without mor-

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or absent.

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bidity. Increasingly, chemotherapy following surgery has become the chosen mode of therapy. The alkylating agents have yielded good remission rates (6–8) but long-term survivors are rare, and half of all patients with disseminated disease will succumb within one year. Attempts to improve the efficacy of chemotherapy (9, 10) include the multiple use of chemotherapeutic agents of different classes in primary treatment such as by Greenspan (11) with the use of methotrexate, an anti-fol, and thio-tepa. In patients who have become refractory to alkylating agents, a triple-therapy regimen of actinomycin-D, 5 fluorouracil and cyclophosphamide has been used by Rutledge (12). Combination chemotherapy may add to the effectiveness of the treatment, but toxicity may also be high. The combination of chemotherapy and radiation has been used (12, 13), but, in general, bone marrow depression is a severely limiting factor to this approach.

Serious cystadenocarcinoma is the most common type of ovarian cancer but the mucinous type may also be present and occasionally predominate. The wide variety of less frequent types such as endometrioid carcinoma, granulosa cell carcinoma or malignant teratoma compound the problem in evaluating therapeutic response. For tumors of marked anaplastic and dedifferentiated histologic patterns of malignancy, the stage of tumor spread is crucial in estimating the lethal potential of the disease.

Although lesions limited to the ovaries (Stage I) are least often seen, they elicit much attention because of the high percentage of long-term survivors. Treatment for this early tumor is complete ovarian ablation, except for some advocates (14, 15) of contralateral ovarian conservation in young women for whom preservation of reproductive potential is important.

The value of postoperative irradiation or chemotherapy in Stage I is equivocal since surgical removal alone is highly but not universally successful in the cure of this group. Occasionally, small anaplastic carcinomas removed incidentally at hysterectomy for myomata may result in rapid death (16). Conversely, despite extensive peritoneal implants, the removal of ovarian tumors of borderline or low histologic malignancy can lead to prolonged or permanent remission (17).

The critical problem in ovarian carcinoma is the treatment of Stage II, III and IV disease with histologic grading of II or III. The five-year survival rate for disseminated ovarian carcinoma is variously reported as being from 10 to 50 percent, although it is difficult to compare the many series in which various types and stages are included.

Controls

In evaluation of the success, however limited, of the present plan of management with postoperative chemotherapy, the problem of a control series is evident. Since long-term survivors are not equivalent to cures, and these survivors were but a small group, there is no simple basis for demonstrating the superiority of the combined surgical chemotherapy approach. Because our early experience with postoperative thio-tepa therapy demonstrated remissions, we felt that it was improper to withhold a potentially helpful therapy for this grave disease. Our continuing experience has reinforced this view. Also, the difficulty in selecting cases of comparable age, stage, and histology, precludes valid controls. Therefore, we have not been able to collect a matched control series.

For comparison to results prior to the use of chemotherapy, reference is made to the work of Munnell and Taylor (18). Their series included patients with ovarian carcinoma treated with surgery alone and surgery followed by radiation. For papillary serous cystadenocarcinoma of histologic Grades II and III, there were at least 43 patients in the current Stages II, III and IV, and only one survived five years (having received radiation therapy). The long-term survivors of our report were patients with high grade histologic malignancy of advanced stage and demonstrated the efficacy of thio-tepa chemotherapy.

Material and Method

Our own experience in the management of disseminated ovarian carcinoma is based on the treatment of 225 patients. The age distribution peaks in the sixth decade and, almost all are between 40 and 75 years of age. The vast majority were in Stage III with but 4 in Stage II and 25 in Stage IV. Serous cystadenocarcinoma was the most common histologic pattern but the other types were represented, although endometrioid was recognized infrequently. Tumors of yolk sac-entodermal sinus and gonadocytoma derivation have been seen, but extremely rapid progression of disease in these patients has not permitted a complete course of treatment and they are not included.

Patients with suspected ovarian carcinoma were hospitalized for evaluation of medical status and tumor spread. Hematologic and chemical determinations, as well as roentgenologic studies of the chest, urinary system, and intestines, were made. Upon completion of these studies, abdominal exploration was performed, with the extent of operation being determined by the spread of the disease as listed below:

Operation	*Percentage of Patients*
Hysterectomy, bilateral salpingo-oophorectomy	30
Omental biopsy	28
Bilateral salpingo-oophorectomy	23
Unilateral salpingo-oophorectomy	12
Paracentesis	5
Lymph node biopsy	2

The intent was to remove the entire tumor by hysterectomy and bilateral salpingo-oophorectomy, or to remove as much of its mass as was feasible without jeopardy to the patient. Biopsy alone was performed when massive disease made a more extensive operation impossible. In patients who underwent lymph node biopsy or paracentesis, there was subsequent abdominal exploration in each case. Five to ten days after operation, chemotherapy with the alkylating agent, thio-tepa (triethylene thiophosphoramide) was started. The initial course was 150-200 mg, given in intravenous daily doses of 10 mg, for five days each week. A subsequent maintenance dosage of 10 mg was given weekly. Bone marrow study was made before the start of therapy and each individual dose of thio-tepa was preceded by complete blood and platelet counts. Leukopenia with a total white cell count of less than 3000, thrombocytopenia with a platelet count of less than 100,000, or anemia with a hemoglobin of less than 8 g were each considered significant toxicity as well as an indication to discontinue therapy. The medication was restarted when these parameters of bone marrow function improved.

Enzyme Studies

Alteration in the level of serum enzymes has been increasingly utilized for diagnosis and prognosis in many diseases (19–21). The mechanism of the release of enzymes into serum is not clear. If cells are injured, enzymes are lost to surrounding body fluids and blood where they are detectable. Cancer cells may produce such injury and, in addition, elaborate excessive enzymes on their own. Necrosis of normal or cancerous tissue is probably not necessary.

Studies (22) were undertaken to determine whether patients with ovarian carcinoma would reveal a characteristic pattern of serum enzyme changes and whether progression or regression of malignant disease following chemotherapy would be reflected by this pattern (23–25). The serum enzymes assayed included lactic dehydrogenase (LDH), glutamic pyruvic transaminase (SGPT), glutamic oxaloacetic transaminase (SGOT), malic dehydrogenase (MDH), aldolase (ALD), enolase (ENOL), pyruvic kinase (PK), myokinase (MK), phosphoglyceryl kinase (PGK), glyceraldehyde phosphate dehydrogenase (GPDH), hexokinase (HK), creatine kinase (CK), and combined A-glycerophosphate dehydrogenase/trioseisomerase (GDH-Tim). The methods employed have been described (26). Only LDH, MDH, and enolase were found useful in following the course of disease.

Several fairly distinct patterns of serum enzyme activity have been observed with chemotherapy of ovarian carcinoma. In the first group, an initial high level of serum enzyme activity showed prompt regression to lower levels under therapy with concomitant regression of tumor. Changes are occasionally detected before clinical improvement is observed.

A second pattern of enzyme change is a pretreatment intermediate elevated level which, despite therapy, rises to even higher levels. This pattern may reflect the lack of therapeutic effect.

A third pattern of enzyme change observed in a few patients was that of initial intermediate values that remain relatively constant despite the progression of disease to the death of the patient.

A clue to these apparently paradoxical results is the high enzyme content of the ascitic fluid, which requires repeated abdominal tapping. The absolute enzyme content of the ascitic fluid is great and the sum of enzyme activity in ascitic fluid and blood serum is very high. Thus, serum values may fail to rise because of the high amounts of enzyme pooled in ascitic fluid.

A fourth enzymatic pattern is that of relatively stable enzyme values with stable clinical course. Such a pattern may represent that restraining influence of chemotherapy on tumor growth.

The four enzyme patterns probably represent variations of one mechanism, depending on various factors: 1) the base level of serum enzymes prior to the development of a tumor; 2) the stage of the malignancy; 3) the histologic type; 4) the response of the tumor to chemotherapy; and, 5) the distribution of enzyme in serum, tissue and ascitic fluid.

Results

Evaluation of response was made by a team of gynecologists, internist, and pathologist, and the clinical management rested with the same group. Two criteria of remission were used: first, greater than 50 percent diminution of tumor mass; and second, complete disappearance of serous effusion. Subjective improvement, possibly a result of close medical supervision and attentive care, was not considered a measurable biologic response. Recurrence of ascites or pleural effusion often signalled the terminal phase of the disease. Bloody ascites was found to be a grave prognostic sign, while great ascitic volume alone was of less importance. Tumor nodules at the site of paracentesis were also associated with rapidly progressive disease.

Objective signs of remission were noted in almost two-thirds of the patients treated, with just over half of all patients demonstrating toxicity. The following list shows the lack of relationship of toxicity to remission.

Status	*Percentage of Patients*
Remission with toxicity	37.5
Remission without toxicity	26.5
Toxicity without remission	15
No remission, no toxicity	21

Although just over half of all treated patients exhibited toxicity by our criteria, almost all experienced moderate depression in white blood cell and platelet counts. Despite this high rate of response to treatment for short periods, one-fourth of all patients were dead within nine months and one-half shortly after one year. The surviving one-fourth, at 21 months, as a group, did remarkably well during the ensuing months, although no common factor was found to distinguish them from those of lesser survival time. Overall 5-year survival was less than 10 percent (Fig. 1). The average length of remission was 15.3 months, but this figure includes a small group of patients with unusually long remissions.

In an attempt to find clues to improving management, we have subdivided our patient group and examined its experience. Survival curves were constructed on a percentage basis for subgroups which were determined by the presence or absence of remission and toxicity. The appearances of remission and toxicity seem unrelated, as there were sizable groups with either one, or both, or none. Thus, the lack of selective drug effect on tumor as compared to hemato-

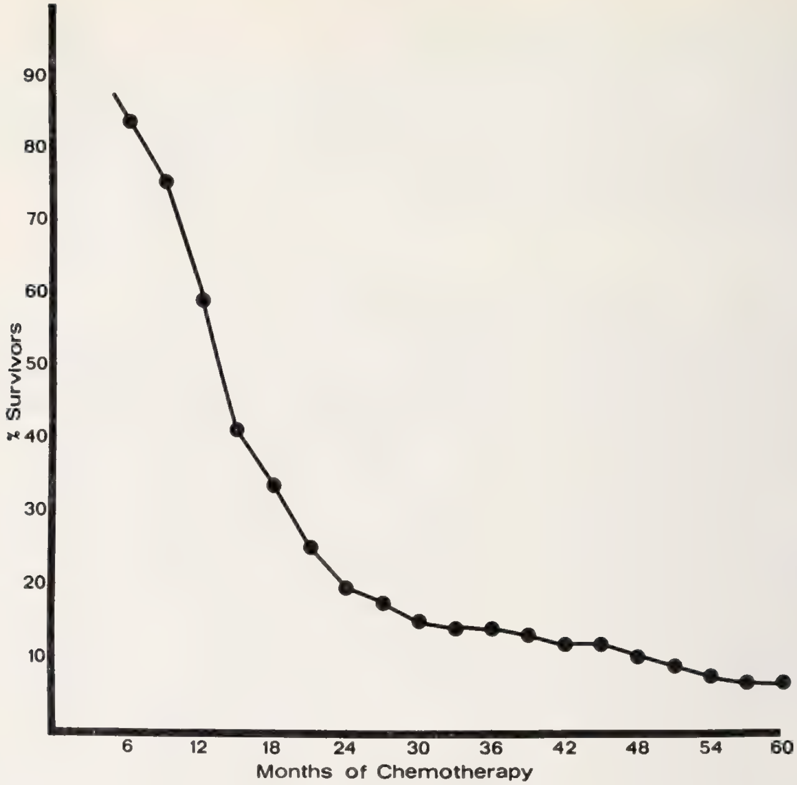

FIG. 1. Total decreasing cumulative survival curve.

poiesis makes it impossible to know whether a patient will have remission or toxicity, or both, as a result of chemotherapy.

The group of all patients with objective remission did have an improved survival curve as contrasted with the group with no remission (Fig. 2). Although this might be anticipated, there was really no deductive reason to justify the assumption, and the survival curves do offer the suggestion that a patient who has a remission under chemotherapy will have increased survival. The same was not true for the total toxic group when contrasted with those not toxic (Fig. 3). These survival curves are intertwined and represent almost identical outcomes for these groups. Toxicity is, therefore, not an indicator of good chemotherapeutic response leading to improved survival. Further breakdown was made in order to examine the survival of patient groups with remission or toxicity alone, remission and toxicity together, or absence of both. Two pairs of survival curves emerge (Fig. 4). Each pair resembles the curve derived on the basis of the single factor of remission. Again, the appearance of remission is related to an improved survival pattern, while toxicity appears to influence neither survival expectancy, appearance of remission, nor length of remission when present.

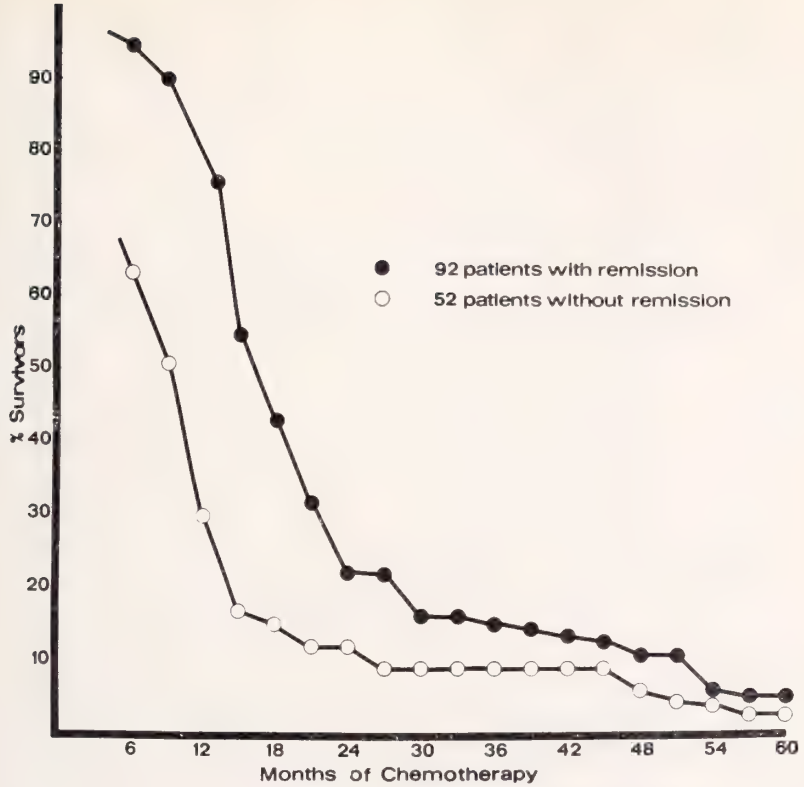

FIG. 2. Comparison of survival curves for patient groups with and without remission.

The Second Look

The promise of chemotherapy has not been fulfilled, and ovarian carcinoma is increasingly important as a cause of death in women (27, 28). With this in mind, and in an attempt to salvage however small a group, we performed a second-look operation in selected patients having non-resectable disease at the time of the initial operation.

Wagensteen popularized the second-look operation (29, 30) for malignant disease of the abdomen chiefly arising in the stomach or colon, and asymptomatic at the time of the second operation. About half were found to harbor residual lymph gland metastases and in these, 9 percent were salvaged. A similar approach was advocated for ovarian carcinoma with less success. Parks (31) and then Corscaden (32) reported six patients in whom inoperable carcinoma of the ovary was found. Following radiation, complete removal of the tumors was possible with good results in four. All of these patients, however, had a borderline histologic type of malignancy. Kottmeier (33) has performed an operation after radiation therapy for fixed disease but concludes that the value of such a procedure is difficult to estimate. In the series of Rutledge and Burns (27), 12 of 288 patients with advanced carcinoma of the ovary under-

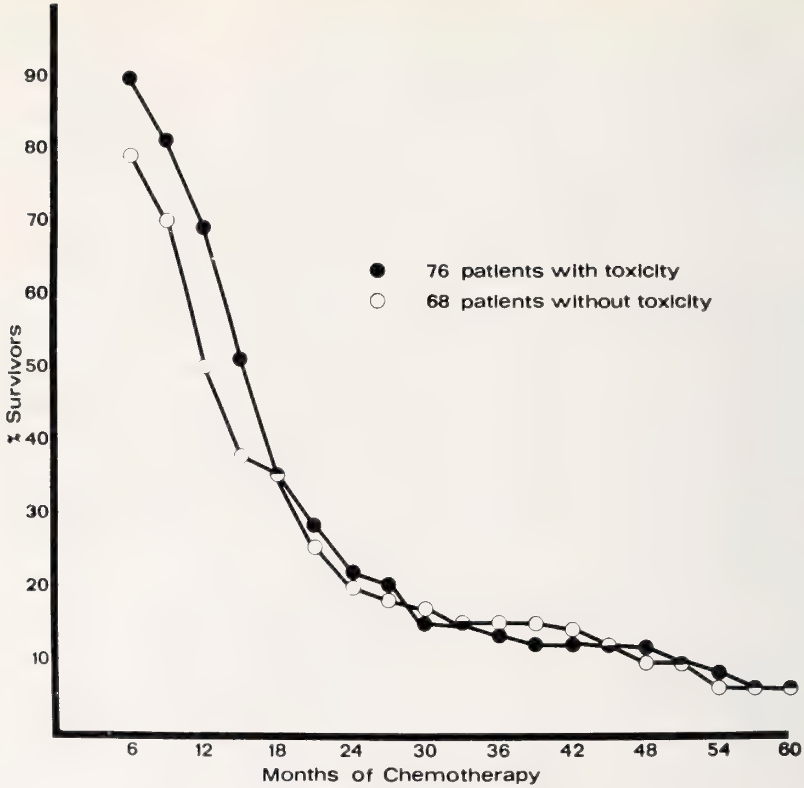

FIG. 3. Comparison of survival curves for patient groups with and without toxicity.

went reexploration. Eight had been treated with phenylalanine mustard and four others with this drug and radiation. A patient with retained ovaries and one with ovaries removed, despite no tumor having been found at reexploration, required treatment for subsequent recurrent disease. Tepper (34) reported a series of 17 patients with advanced ovarian carcinoma who had exploratory laparotomy, 3000 rads radiation, thio-tepa and second-look surgery. A three-year survival of four patients is reported, although histologic grading is not stated.

In our own experience, after chemotherapy with thio-tepa, a second-look operation was performed in eight patients who initially had disease of clinical Stages III or IV, and Grade 3 histologic malignancy. Six other patients required additional abdominal operations for the relief of intestinal obstruction not responding to conservative treatment, but these are not considered as second-look operations.

The second-look operation was performed in three situations. First, it was carried out in patients with retained ovaries and complete tumor disappearance. Chemotherapy permitted a complete operation, and good results were obtained. Second, it was done in patients with remaining ovarian tissue and clinically

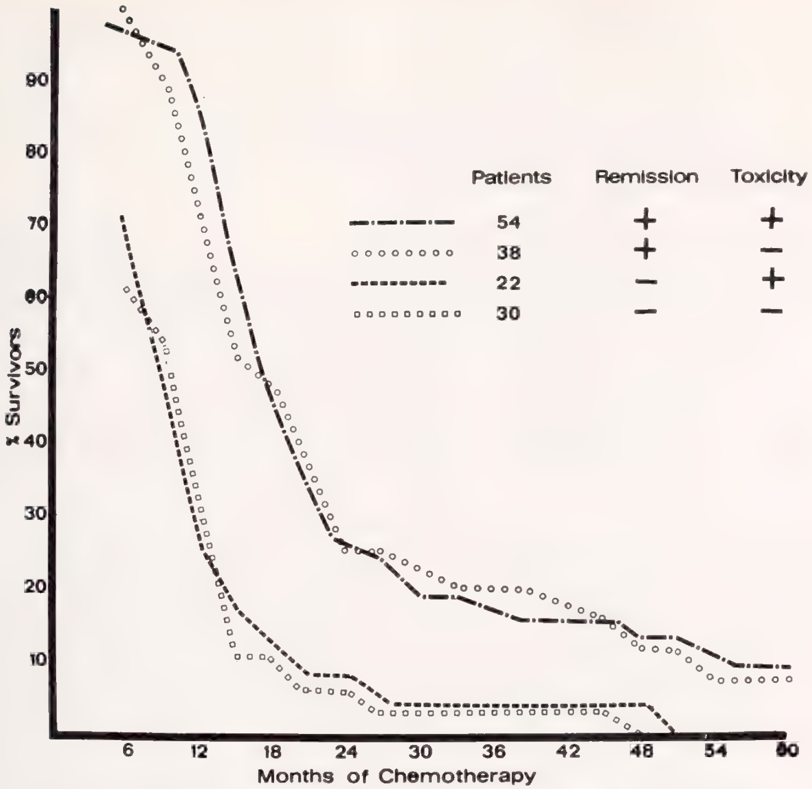

FIG. 4. Survival curves for groups with remission and toxicity, singly or jointly, present or absent.

appreciated residual tumor; complete removal at reexploration was not possible and these patients did poorly. Third, the procedure was performed in patients with previous removal of ovaries but residual tumor; complete removal was impossible and no improvement resulted.

In the fourth possible situation, previously removed ovaries without residual tumor, a second-look procedure was not performed because of our current conviction that chemotherapy should be continued for life in those patients with initially disseminated disease. Careful abdominal vaginal and rectal examinations for nodular masses is an effective method for the detection of recurrent disease, and close scrutiny of bone marrow function parameters is mandatory.

An unusual outcome following reexploration included one patient who had an omental biopsy of nonresectable tumor at initial operation. Chemotherapy yielded marked diminution of tumor masses and disappearance of ascites. One year later, repeat surgery was necessary for an enlarging tumor mass causing sigmoid-colonic obstruction by pressure but not invasion. Following removal of the ovaries, with continued chemotherapy, the patient did well for 13 months, but then had multiple recurrences leading to death.

On the basis of this experience, the second-look procedure for carcinoma of the ovary, Stages II, III or IV, should be performed for that small number of patients with initial, nonresectable disease in which the ovaries have been left and complete clinical regression is noted under chemotherapy. In view of the last case described, an occasional case with retained ovaries and known residual disease may profit from a second-look operation.

Conclusion

In advocating the use of chemotherapy for ovarian carcinoma, several reasons take greatest weight. First, the management of patients receiving alkylating agents is now of sufficient sophistication so that the hazard of drug toxicity has been lessened to an acceptable level. Second, the accumulation of a group of long-term survivors, greater than expected without this therapy, offers individual patients at least some small chance. Third, the high rate of objective remission (almost two-thirds of the present series) gives many patients a comfortable respite.

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Diagnosis of Pericardial Effusions and Cardiac Enlargement Using 99mTc-Pertechnetate and the Multiple Crystal Rectilinear Scanner

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Confirmation of suspected pericardial effusions and their differentiation from cardiac enlargement has been traditionally accomplished by manipulative radiologic techniques such as contrast angiography or intrapericardial gas instillation. The development of diagnostic ultrasound and radioisotope blood pool imaging techniques enables the physician to confirm the presence of a pericardial effusion or cardiac enlargement with virtually no risk or discomfort to the patient. This paper describes a modification of the standard blood pool imaging techniques which yields high quality scans in a short period of time. This procedure, which takes less than five minutes, combines the superior resolution of the rectilinear scanner with high count rates and excellent statistics obtained using usual doses of 99mTc as the pertechnetate, and rivals the speed of the gamma camera.

Radioisotope blood pool imaging entails the administration of an appropriate radiopharmaceutical followed either by rectilinear scanning or serial and/or composite pictures from a flow study taken on a gamma camera. The cardiac, pulmonary, and hepatic blood pools are visualized on the scans; a space separating the cardiac blood pool from the pulmonary and hepatic blood pools is suggestive of a pericardial effusion. Cardiac enlargement appears as a significent increase in the transverse diameter of the cardiac blood pool. The rectilinear scanner yields pictures with excellent spatial resolution, but the technique is time-consuming (30–40 minutes) and is preferably performed with radioactive compounds which are primarily located in the blood pool, such as radioiodinated human serum albumin (1) or human serum albumin tagged with technetium-99m (2). It is possible to use technetium-99m as the pertechnetate in such studies (3); however, by the time the rectilinear scan is completed a substantial portion of the radioactivity will be located outside the blood pool. The gamma camera technique, on the other hand, is rapid and may be adequately performed with technetium-99m pertechnetate (4, 5). However this approach suffers from the inherently coarse resolution of the gamma camera and the poor counting statistics of dynamic studies performed with reasonable amounts of technetium-99m. Using the multiple crystal rapid scanner (Dynapix®), we have adapted the rectilinear scanning technique to minimize many of the drawbacks of the above methods.

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Materials and Methods

The patient is positioned under the ten detector probe of the Dynapix® with the high energy five-inch focus collimator in place. Nine to ten millicuries of technetium-99m pertechnetate are rapidly administered into an antecubital vein with the tourniquet in place. At the completion of the injection the tourniquet is released, and the scan is started 150 seconds later. The following settings of the Dynapix® controls are used: speed 3.0 cm per second; X increment 0.2 cm; Y increment 0.3 cm (8 lines); peak energy 140 kev; window plus or minus 30 kev; differential 36; and suppression 12. The scan is recorded on digital magnetic tape for possible later replay of the data to optimize the picture. However, using the settings outlined above, such replay has rarely proved to be necessary. Scan presentation is on Polaroid® color film with black representing the background or suppressed counts. On this presentation the range from minimum to maximum counts is displayed as a color spectrum in which violet represents minimum count rates and deep red represents maximum count rates (Fig. 1). There is a one to five linear minification ratio from the patient to the finished print.

Twenty-five persons undergoing routine brain scans with technetium-99m pertechnetate, who had no clinical, laboratory, or radiologic evidence of cardiovascular disease, comprised the normal group. Fourteen patients referred for blood pool scans for evaluation of cardiac enlargement on X-ray made up the patient group. Several of these patients underwent blood pool scanning with radioiodinated serum albumin as well.

Results

Normals: In all normal subjects the scans were comparable to that shown in Figure 1. Invariably, the lower border of the visualized cardiac blood pool was contiguous with the upper border of the hepatic blood pool. When the pulmonary blood pool was clearly visualized, it was also contiguous with the cardiac blood pool.

Patients with pericardial effusions: The presence of a suspected pericardial effusion was confirmed in seven patients. In each case, the scans of these patients showed a definite space separating the cardiac blood pool from the pulmonary and hepatic blood pools. Repeat scans, after removal of pericardial fluid by pericardiocentesis, no longer demonstrated this space. A typical scan in a patient with an effusion is shown in Figure 2. This seventeen-year-old girl, admitted in congestive heart failure, proved to have a tuberculous pericardial effusion. The scan (Fig. 3) performed after the removal of about 400 cc of effusion fluid by pericardial tap was normal. The hepatic enlargement seen on the first scan, and presumed to be due to congestion secondary to tamponade, was not seen on the post-tap scan.

An unusual case was that of a sixty-three-year-old man in congestive heart failure with a markedly enlarged cardiac shadow on X-ray (Fig. 4). His aortic valve had been replaced with a prosthesis several months earlier. Blood pool scans performed by the conventional radioiodinated serum albumin technique (Fig. 5) and with technetium-99m pertechnetate (Fig. 6) were comparable; they showed the presence of a significant space separating the cardiac from the pulmonary and hepatic blood pools. A discrete area of significant accumulation of radioactivity was noted to the right of the superior portion of the cardiac blood pool; this was interpreted as a possible pulmonary artery aneurysm. At autopsy the patient was found to have a right pulmonary artery tear into an aneurysmal sac and the pericardial space was filled with much clotted blood; this mass of clotted blood measured about 3 cm in thickness, correlating well with the findings on scan.

Patients with cardiac enlargement: Seven patients suspected of having a pericardial effusion proved to have cardiac enlargement. All had increased cardiac blood pool diameters and increased cardiothoracic ratios on scan, as in the representative case shown in Figure 7. In each patient the measurement of the cardiac blood pool correlated well with the actual measurement of the cardiac shadow on the chest radiograph (Fig. 8). Cardiothoracic ratios measured on the scan and on the chest film were in close agreement. Other pertinent diagnostic modalities were applied to each of these patients; in all seven cases the scan diagnosis was confirmed.

Discussion

The technique described above allows the visualization of the cardiac, hepatic, and pulmonary blood pools with a single injection of a commonly available radiopharmaceutical. The inherent resolution of a rectilinear scanner coupled with the excellent photon yield of technetium-99m pertechnetate gives a high quality scan in a short period (under five minutes) from the time of injection. Indeed, the temporal relationship between the time of injection and the time of scanning is of utmost importance in this technique. The scan must be performed after essentially complete mixing of the radioactive material with blood has been achieved. A scan started sixty seconds after injection rather than one hundred and fifty seconds after injection will distort radioactivity in the cardiac blood pool and will not clearly visualize the liver blood pool. If the scan is started more than about four minutes after the injection, the technetium may no longer be primarily located intravascularly, and the blood pools may be poorly visualized. Such delayed scans show that a good portion of the material has localized in other organs of the body such as the stomach (Figure 9), salivary glands and thyroid.

The temporal characteristics of pertechnetate distribution also apply to blood pool scans performed with a conventional rectilinear scanner. The use of RISA for blood pool visualization obviates these problems of distribution but increases the time required to obtain an adequate scan and subjects the patient to a greater radiation dose. Though technetium-99m labeled serum albumin combines the advantages of RISA with those of pertechnetate, its preparation requires a moderately sophisticated radiopharmaceutical facility; this is not necessary when technetium-99m pertechnetate is used.

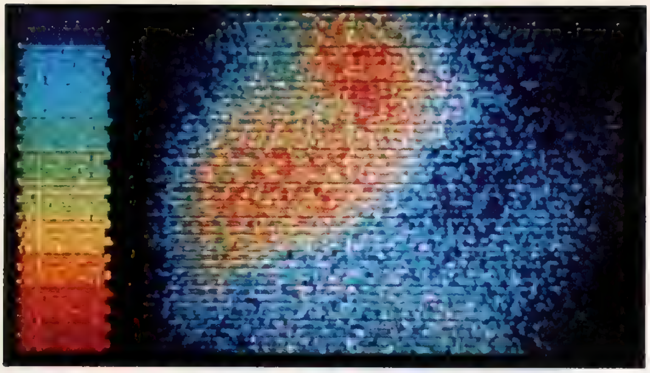

Figure 1. Cardiac, hepatic and pulmonary blood pool scan (10mCi 99m-Tc) in a normal patient. The spectrum to the left of the scan illustrates the color display from minimal radioactivity (violet) through maximal radioactivity (deep red). Each succeeding color represents a 10% change in count rate above background (black).

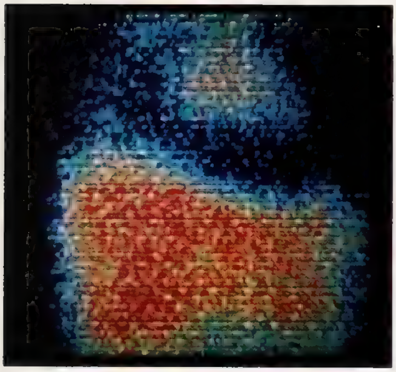

Figure 2. Cardiac, hepatic and pulmonary blood pool scan (10mCi 99m-Tc) in a seventeen year old patient with a pericardial effusion.

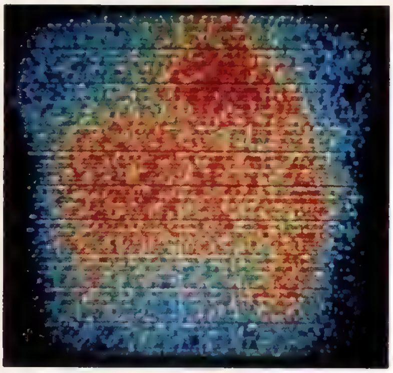

Figure 3. Cardiac, hepatic and pulmonary blood pool scan (10mCi 99m-Tc) after pericardiocentesis and removal of 400cc's of fluid (same case as in Figure 2).

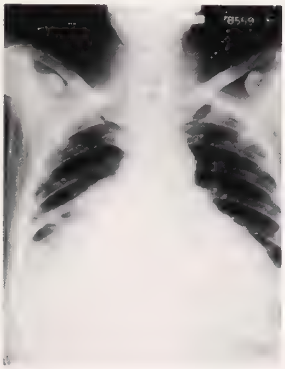

Figure 4. Chest radiograph of a sixty-three year old man with a pericardial effusion and right pulmonary artery aneurysm.

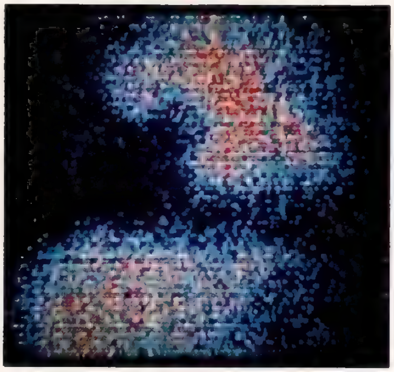

Figure 5. Cardiac, hepatic and pulmonary blood pool scan (500μCi 131-I human serum albumin) in a sixty-three year old man with a pericardial effusion and right pulmonary artery aneurysm (same case as in Figure 4).

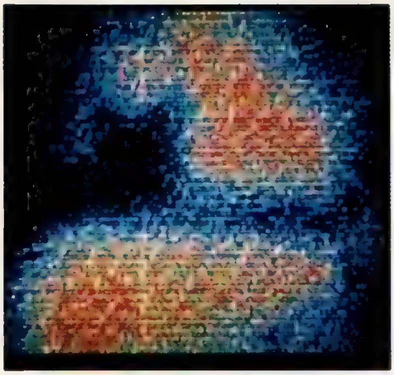

Figure 6. Cardiac, hepatic and pulmonary blood pool scan (10mCi 99m-Tc) in a sixty-three year old man with a pericardial effusion and right pulmonary artery aneurysm (same case as Figures 4 and 5).

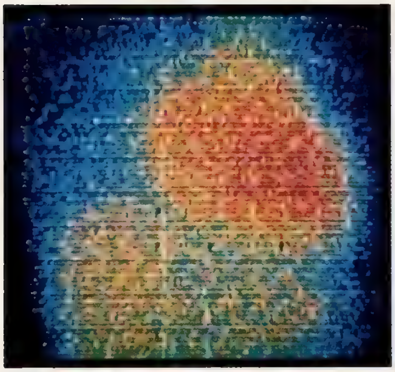

Figure 7. Cardiac, hepatic and pulmonary blood pool scan (10mCi 99m-Tc) in a patient with marked cardiomegaly.

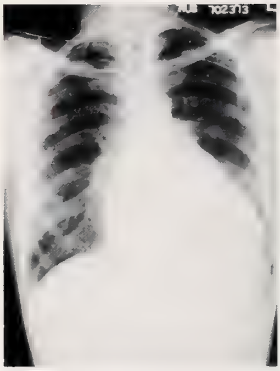

Figure 8. Chest radiograph of a patient with marked cardiomegaly (same case as in Figure 7).

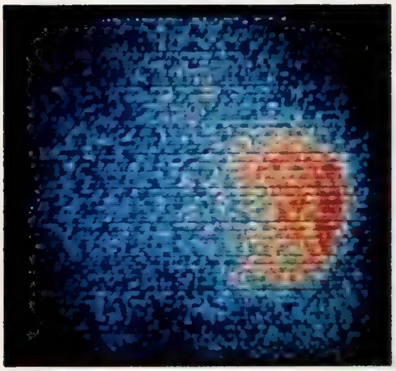

Figure 9. Cardiac, hepatic and pulmonary blood pool scan (10mCi 99m-Tc) started eight minutes after the administration of technetium. Note that the blood pools are poorly visualized; most of the radioactivity is in the stomach.

These study reproductions have been supplied through the courtesy of Picker Corporation. They are reproductions of radioisotope scans produced by a Colorpix™ 2 Rectilinear Scanner.

Other techniques for blood pool visualization and pericardial effusion diagnosis utilizing technetium-99m pertechnetate have been described (4, 5). Those techniques require the use of camera-type devices in the dynamic mode. Under these circumstances, the poor resolution of a camera device vis-a-vis a rectilinear scanner is compounded by the poor counting statistics of the serial or composite scintiphotographs derived from such studies. Some workers have attempted to minimize this problem by using doses of technetium-99m that are two to three times greater than were used in this study; the resulting improvement does not appear to be commensurate with the increased radiation exposure to both patient and staff.

The focusing rapid rectilinear scanner collimator best visualizes the plane at which a separation between the cardiac and hepatic blood pools is of greatest significance and where artifacts are minimal. The collimators of gamma-imaging devices are of nonfocusing design. Attenuation of photon yield is primarily dependent on the inverse square law; pools of radionuclide closer to the camera collimator face are more prominently displayed than those farther away. There is evidence, in keeping with these considerations, that camera devices may frequently indicate spurious or non-existent separations between the cardiac and hepatic blood pools (6).

Pericardial effusions are not a common pathologic entity, and the number of cases we have studied to date is not large. However, there is an obvious difference between the scans of the normal subjects and patients with pericardial effusions. Moreover, after successful treatment of an effusion, the scans reverted to normal, clearly demonstrating the usefulness and validity of this technique. All patients studied who had large cardiac shadows on X-ray were shown to have either a pericardial effusion or marked cardiac enlargement by this technique. In no case did subsequent diagnostic studies or the clinical course contradict the findings on scan.

The rapidity of the procedure and the minimal patient manipulation involved allows it to be applied to the severely ill patient and to the patient who can lie still for only a limited amount of time. Technetium-99m pertechnetate has been used in thousands of scanning procedures and has proven to be a safe radiopharmaceutical. In the doses employed by us the radiation dose is minimal. This radiopharmaceutical is readily available to virtually all nuclear medicine laboratories; in those institutions using the technetium-99m generator the procedure can be made available on an around-the-clock emergency basis.

The relatively simple procedure outlined above should be applicable to many forms of blood pool imaging. It may be possible to differentiate vascular from non-vascular lesions by this technique. At present we are investigating other applications of this technique.

Acknowledgment

This work would not have been possible without the expert technical assistance of Nancy Acheampong, Mary Ahern, Carmen Diaz and Steven Leffler.

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Percutaneous Adrenal Venography in Primary Hyperaldosteronism

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Abstract

Percutaneous catheterization of the adrenal veins was used to study ten patients with primary hyperaldosteronism due to an aldosterone-producing adenoma. The tumor was demonstrated radiographically in six of these patients. In the eight patients in whom the concentrations of aldosterone in the adrenal venous blood was measured the correct location of the adrenal tumor was clearly established. These results indicate that adrenal venography may considerably improve the diagnosis and management of this disorder.

Introduction

Primary hyperaldosteronism can be strongly suspected when benign arterial hypertension coexists with hypokalemia due to renal potassium wasting. The diagnosis can be readily confirmed by demonstrating, that under suitable experimental conditions, the aldosterone production is excessive and the renin angiotensin system is suppressed (1). A major diagnostic difficulty however has been to distinguish patients with primary hyperaldosteronism who have an adrenal adenoma from those with bilateral adrenal hyperplasia (2–4). The current treatment of these two entities differs, adrenalectomy being used when an adrenal tumor is present, while the administration of spironolactone and other antihypertensive drugs appears to be the treatment of choice for patients with bilateral adrenal hyperplasia (2, 3).

A second diagnostic problem in primary hyperaldosteronism has been the localization of the adrenal adenomas. These tumors are almost invariably too small to be detected by traditional radiographic techniques and not unfrequently they are difficult to find even during bilateral adrenal exploration. During the past few years the percutaneous catheterization of the adrenal veins (adrenal venography) has permitted a substantial portion of aldosterone-producing adenomas to be visualized radiographically. Furthermore, the assay of aldosterone in the adrenal venous blood obtained during this procedure has correctly located an even larger number of these tumors. Although not enough data are as yet available, we expect that the concentration of aldosterone in adrenal venous blood will permit the preoperative diagnosis of the bilateral adrenal hyperplasia of primary hyperaldosteronism. We have previously reviewed the current state of adrenal venography and have reported our three-year experience with this technique for the study of adrenal disorders in general (5). In this paper we wish to report briefly our more recent experience with this technique in primary hyperaldosteronism.

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Patients and Methods

Since November, 1968, ten patients with primary hyperaldosteronism have been studied by adrenal venography at our Institution. In all cases benign arterial hypertension, hypokalemia due to renal potassium wasting, excessive aldosterone production, and suppressed plasma renin activity were clearly present.* All ten patients were studied radiographically by the retrograde injection of contrast material into the adrenal veins. In the last eight patients the concentrations of aldosterone were measured in the adrenal venous blood after an assay method was developed for this in our laboratory (6). The details of the radiographic and biochemical techniques have been previously described (5).

Results

Radiographic findings: All ten patients had solitary aldosteronomas at surgery. The tumor was demonstrated radiographically in six of the patients. In one of the four remaining patients the adrenal vein draining the tumor could not be catheterized. Adrenal venography was, however, useful for the management of this patient since typical radiographic findings (7) demonstrated that the other adrenal had been removed during a previous nephrectomy. In another patient, extravasation of contrast material occurred on the side of the tumor and prevented the adequate evaluation of the radiograms. In the two remaining patients adrenal venography was normal bilaterally. These two tumors, which escaped radiographic detection, were both relatively large measuring 1.2 and 1.5 cm in diameter and were buried well inside the adrenal parenchyma. The size of the tumors in the remaining eight patients ranged between 0.7 and 2.3 cm and the two smallest tumors (0.7 cm) were readily recognized radiographically.

Biochemical findings: The table shows the concentrations of aldosterone in the adrenal veins of the eight patients so studied. Using this approach, the tumor could readily be assigned to the correct side in all cases. The concentrations of aldosterone were 20 to 107 times greater on the side of the tumor as compared to the nontumorous side. In subjects without primary hyperaldosteronism the greatest difference noted between the titers in the two adrenal veins was about two-fold. In addition, the concentrations of aldosterone in the nontumorous adrenal veins were invariably much closer to the levels in the peripheral circulation than they were in the control subject. This suggested that aldosterone production was suppressed in the adrenal tissue outside the tumor. The concentrations of aldosterone in the adrenal venous blood draining the tumors were greater than normal in all patients except in R.E., in whom the titer was at the upper limits of the normal range.

Complications: Severe long-lasting flank pain as described by Bookstein et al (8) occurred on the side of the tumor in the first patient studied and was not accompanied by extravasation of radiographic contrast material. Extravasation of contrast material associated with mild flank discomfort was noted in two

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* We are grateful to Dr. Lawrence Krakoff for the determination of some of the plasma renin activities.

TABLE I

Concentrations of Aldosterone in Plasma of Patients with Primary Aldosteronism ($\mu g\%$)

Patient	Inferior Vena Cava	Adrenal Vein		T/NT	NT/IVC	Localization by Xrays
		No Tumor	Tumor			
FA	0.03	0.05	2.99	59.8	1.7	Yes
BL	0.18	0.22	6.30	28.6	1.2	Yes
PM	0.04	0.07	6.06	86.6	1.7	Yes
RE	0.04	0.02	1.10	55.0	0.5	No
SE	0.06	0.22	18.86	85.7	3.6	No
CM	0.03	0.05	5.37	107.4	1.7	Yes
SR	0.02	0.06	1.60	26.7	3.0	No
GB	0.06	0.16	3.13	19.6	2.7	Yes
Primary aldosteronism: mean	0.06	0.11	5.68	58.67	2.01	
Normal: mean (range)	0.015 (0.005–0.02)	0.33 (0.06-1.28)		1.46 (1.03–2.10)	26.0 (8–98)	

additional patients. No clinical or laboratory evidence of adrenal insufficiency was noted following venography. None of the seven aldosteronomas removed at our Institution showed microscopic or macroscopic hemorrhage inside the tumor.

Surgical treatment: Eight of the patients underwent unilateral adrenalectomy through a translumbar approach, while two had bilateral adrenal exploration transabdominally. In all patients adrenalectomy was followed by rapid correction of the electrolyte abnormalities and by a more gradual return of the blood pressure towards normal. In four patients, in whom it was measured, aldosterone production fell nearly to zero postoperatively but none of the patients required replacement with mineralocorticoids or with glucocorticoids.

Comments

Before adrenal venography made it possible to diagnose the underlying adrenal pathology of primary hyperaldosteronism patients with this disorder underwent bilateral adrenal exploration usually through a transperitoneal approach. This surgical procedure is less well tolerated by the patients than unilateral translumbar adrenalectomy. In addition, because of their small size, aldosteronomas were not infrequently difficult to find during surgery sometimes necessitating unwanted bilateral adrenalectomies. In other instances, damage to the vascular supply during exploration of the nonaffected adrenal has led to adrenal insufficiency following unilateral adrenalectomy. These and other difficulties encountered during blind exploration of patients with primary hyperaldosteronism have been well described by Nesbit (9) and by Egdahl (10) among others.

The results described in this paper are similar to those recently reported by three other groups who have compared venographic and surgical findings in patients with primary hyperaldosteronism (11–13). In the experience of these workers between 57 percent (12) and 70 percent (11, 13) of solitary aldosteronomas can be visualized radiographically. Thus, the radiographic findings alone can spare the disadvantages of bilateral adrenal exploration in about two-thirds of the patients. If a tumor is visualized on one side unilateral adrenalectomy by a translumbar approach appears justified since less than 6 percent of aldosteronomas are bilateral (14) and since adrenal venography can demonstrate about two-thirds of such tumors if they are present. The experience of others (11, 12) that the smaller aldosteronomas appear more likely than the larger ones to be missed radiographically was not borne out in our series. Adrenal venography does not appear to be suitable for demonstrating the hyperplasia associated with primary hyperaldosteronism since all of six patients with this entity had normal venograms (12).

In our experience the assay of aldosterone in the adrenal venous blood was more consistently helpful than the radiographic findings since it localized the tumor correctly in all patients. The experience of two of the three above mentioned groups has been similar. Horton and Fink (13) successfully used this approach to assign all of 14 aldosteronomas to the correct side while Kahn and coworkers (12) succeeded with ten of their twelve patients with unilateral adenomas. The latter workers (12) also had the opportunity of studying six patients with primary aldosteronism associated with bilateral adrenal hyperplasia. All six patients had normal radiographic findings. The aldosterone levels were elevated bilaterally in three patients, bilaterally normal in one and elevated on one side only in two. This suggests that with further experience the assay of aldosterone in adrenal venous blood will probably permit the diagnostic separation of patients with primary aldosteronism due to bilateral adrenal hyperplasia from those with tumor. This is desirable since these patients cannot be clearly distinguished by other current diagnostic means and they are not considered candidates for surgery as their hypertension does not benefit significantly from adrenalectomy (2–4). For several reasons the collection of relatively undiluted adrenal venous blood and the accurate assay of aldosterone in plasma are not easy procedures and this may explain why other workers (11) have found this technique unsatisfactory.

As carried out at present at our Institution, adrenal venography causes little discomfort to the patients and is usually completed in less than one hour with about two-thirds of this time being required for the development of the radiographic plates. Its only significant complication has been the formation of intraadrenal hematomas in up to five percent of the patients (5). It appears reasonably clear that this complication occurs when the radiographic contrast material is injected too forcefully and extravasates into the adrenal parenchyma. As was the case in one of our patients, these adrenal hematomas are usually accompanied by severe flank pain lasting up to 48 hours. Much more rarely, there is clinical or laboratory evidence of adrenal insufficiency, usually of a transitory nature. This complication appears to have become less frequent with better experience and we have not encountered it during the past two years. In most cases, the diagnosis of primary aldosteronism can confidently be made on clinical grounds alone (15, 16). The other syndromes of mineralocorticoid excess, also characterized by benign hypertension and spontaneous hypokalemia, are very rare and usually present easily recognizable clinical features (17). For this reason, we suggest that, if typical clinical features are present, catheterization of the adrenal veins may be carried out without waiting for the results of other time consuming diagnostic procedures such as the aldosterone secretion rate and the plasma renin activity.

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Persistent Left Superior Vena Cava as a Complicating Feature of Transvenous Cardiac Pacing

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The blind, or floating, technique for insertion of a temporary cardiac pacemaker by the transvenous route has been widely accepted as a successful mode of treatment of bradyarrhythmias complicating myocardial infarction. Its acceptance is due to simplicity of insertion, ease of handling, and high incidence of successful pacing. It is particularly helpful in institutions where a portable image intensifier is not available to the acutely ill patient.

This article reports an unusual but not rare congenital anomaly of venous return which may complicate the procedure and which may result in difficulty of insertion and in possible loss of pacemaker capture. The diagnosis in this case was made during life, whereas the one previous report of a similar anomaly was diagnosed only at postmortem examination, where death was due to pacemaker failure (1).

Case Report

A 56-year-old white man was admitted to the Coronary Care Unit of the Jewish Memorial Hospital with acute precordial pain radiating to the left shoulder, associated with sweating. There had been no history of angina pectoris, hypertension, or any other significant illnesses. Duration of pain before admission was approximately two hours.

On physical examination the patient was diaphoretic and appeared in acute distress. There was no evidence of congestive heart failure. There were no rales in the chest. The heart rate was 88 per minute and was regular. The blood pressure was 150/90. Heart tones were of normal quality. There were no murmurs and no gallop rhythms audible.

Electrocardiogram showed evidence of acute anteroseptal wall myocardial infarction associated with right bundle branch and left anterior hemiblock pattern—that is, partial bilateral bundle branch block pattern (2). A portable x-ray of the chest was interpreted as normal.

In the first 24 hours, the patient developed transient atrial fibrillation interspersed with episodes of marked sinus bradycardia, sinus arrest and periods of Mobitz II block. The decision was then taken to pace transvenously. An attempt was then made to pass a No. 4 F Bi-polar cardiac pacing catheter through a right subclavian vein puncture. It was apparent that the pacing wire entered the vein only for a distance of approximately 4 to 5 centimeters and then appeared to meet an obstruction and failed to pass into the heart. For this reason, a left subclavian puncture was promptly performed and a similar No. 4 F Bi-polar transvenous catheter passed through the left subclavian vein. This, by contrast passed easily and promptly initiated ventricular capture. A standard 12 lead electrocardiogram was then taken and demonstrated pacemaker rhythm with complete capture and the pattern of a left bundle branch block with marked left axis deviation, indicating that the pacemaker was pacing the right ventricle at the lower portion of the intraventricular septum. Procedure was then terminated and a routine portable chest x-ray was taken to establish the position of the pacing wire. This position is shown in Figure 1. As apparent, the wire takes an unusual course, passing down along the left cardiac border, into the center of the cardiac silhouette where the tip is obscured by the density of the spine. On the basis of this chest x-ray, the diagnosis was then made of persistent left superior vena cava entering the coronary sinus,

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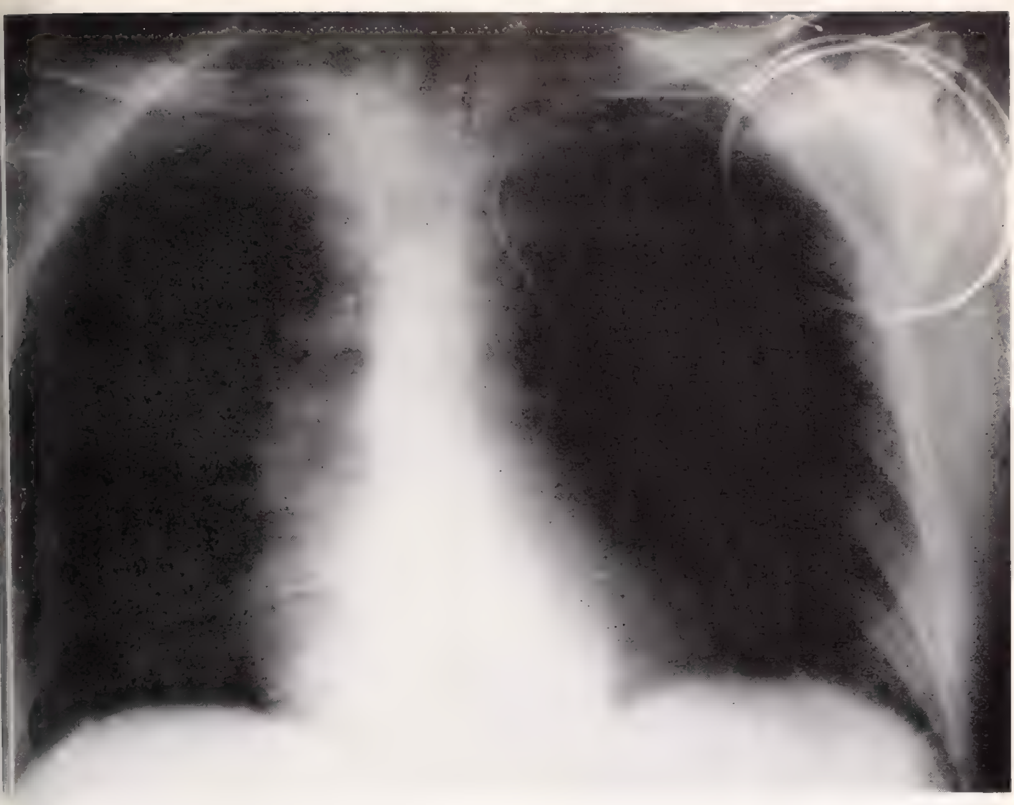

FIG. 1. Note the unusual course of pacemaker wire along the left border of cardiac silhouette curving toward the midline. The position of the tip of the wire is not visualized, but was demonstrated by electrocardiogram to be pacing the apex of the right ventricle.

and it was the impression that the pacing catheter entered the right ventricle across the tricuspid valve to pace the right ventricle near the apical portion of the intraventricular septum. Venous angiography was then performed shown in Figure 2, confirming the diagnosis. In addition, it showed an unusual variant of the superior vena caval anomaly, namely a complete absence of the normal right superior vena cava with entire drainage of the right subclavian and innominate veins into the persistent left superior vena cava. Demand pacing was continued in this patient for a period of two weeks. After one week, the patient ceased to show evidence of atrial fibrillation or sino-atrial arrest, and evidence of heart block disappeared. Temporary transvenous pacemaking was then discontinued and patient continued to do well, thereafter. Because of the nature of the anomaly, it was then decided not to carry out permanent transvenous pacing in this patient.

Discussion

The incidence of persistent left superior vena cava in the general population has been estimated at 0.5% (3). In patients with known congenital heart disease, it has been estimated at 10% (3). It is, therefore, apparent that this anomaly will be encountered in increasing numbers as more and more patients are subjected to transvenous pacing. Fortunately, the anomaly presented in this

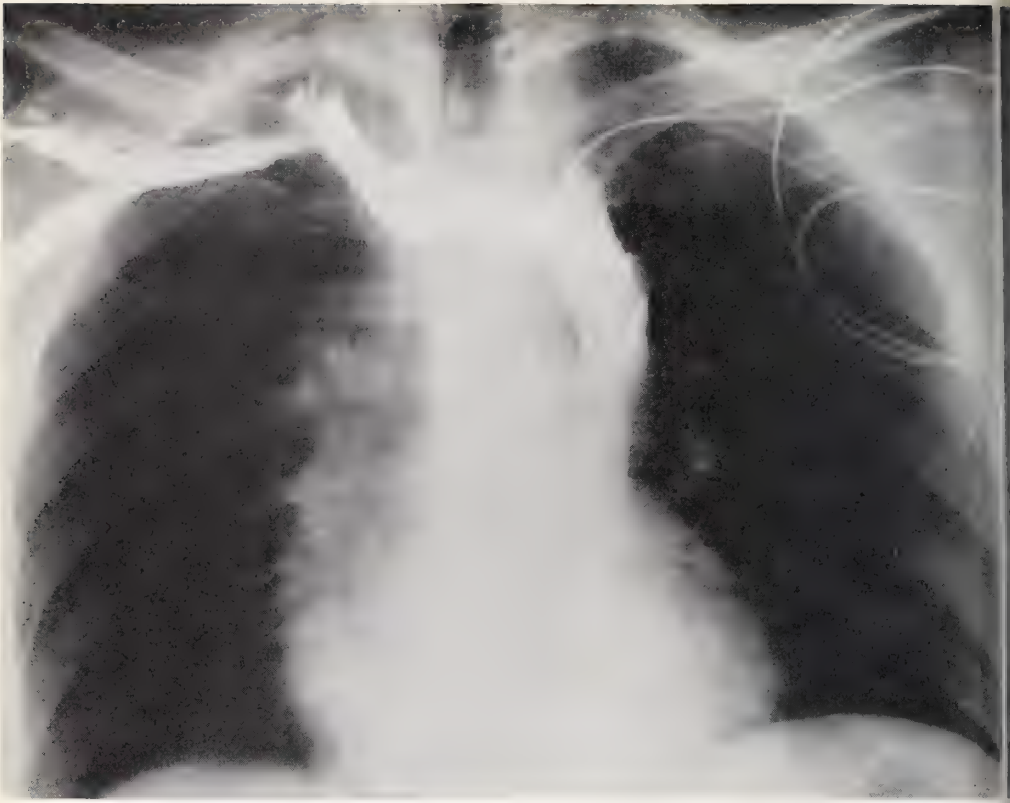

Fig. 2. Angiocardiogram is made from right brachial vein. The right subclavian vein is opacified and a bridge joins the left superior vena cava. The normal right superior vena cava is absent. Pacemaker wire is seen descending in the left superior vena cava.

case, that is, the combination of a persistent left superior vena cava with absence of right superior vena cava is rare as evidenced by the fact that only 32 cases have been reported (1). In four of these, on postmortem examination, a nonfunctioning right superior vena cava was identified as atrophic chord (4). The problem which this anomaly presents to adequate transvenous capture is the fact that the left superior vena cava commonly enters into the coronary sinus. From the coronary sinus, it is then difficult but not impossible, to direct the catheter into the right ventricle for appropriate pacing (1, 5, 6). This, however, would require that the pacemaker be inserted under direct fluoroscopic control. Rarely, a persistent left superior vena cava may enter the left atrium and in such cases one may inadvertently pace the left ventricle (7). Twenty-two cases of this latter condition have been reported (8). All such patients have presented with central cyanosis. While the diagnosis in this case was made by the position of the pacing wire, it may be suspected from the routine chest film where the aberrant vessel appears as a flat, broad band of medium density running vertically downward along the left border of the superior mediastinum.

The embryology of this condition and its various forms have received several reviews (6, 9).

Summary

A case has been presented illustrating a rare congenital anomaly of venous return which complicated the procedure of transvenous cardiac pacemaking. It is hoped that the description of the catheter course and of the angiography presented will help to elucidate similar cases that may be encountered in the future.

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Malabsorption and Metastatic Melanoma

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DANIEL H. PRESENT, M.D.

Abstract

Severe malabsorption resulting from extensive involvement of the small intestine by metastatic melanoma is described. Bacterial overgrowth on the surface of the tumor nodules and replacement of the bowel by the neoplasm were both thought to be responsible for the absorptive defect.

Introduction

Intestinal malabsorption is a manifestation of many disease processes. Other than lympho-reticular diseases, neoplastic infiltration of the bowel has not, to our knowledge, been implicated in its pathogenesis. This report concerns a patient in whom malabsorption was the presenting symptom of a metastatic melanoma of the small intestine. The possible mechanisms by which malabsorption was produced in our case are briefly discussed.

Case Report

A 58-year-old woman presented with a chief complaint of diarrhea of three to four weeks' duration. She stated that she had six to nine soft to semi-liquid, brown stools per day. They did not float and were not foul smelling. The patient also complained of fever from 101° to 103°F, occurring predominantly at night and occasionally associated with chills. The patient denied having nausea, emesis, hematemesis, melena, jaundice, tuberculosis, diabetes, or weight loss. History included the removal of a melanoma from the back 16 years previously.

Physical examination revealed a pale, thin, white woman with a blood pressure of 130/80 mm Hg, a pulse of 90/min., a respiratory rate of 20/min, and a temperature of 98.6°F. Palpation of the neck revealed an egg-shaped mass in the submandibular region on the right side. No other adenopathy was noted. The heart and lungs were normal to percussion and auscultation. The abdomen was nontender, and soft. Bowel sounds were hypoactive and the liver and spleen were not palpable. A rectal examination was normal. The stool was 4+ guaiac positive. Cultures of the stool, blood, bone marrow, and urine were repeatedly negative.

Laboratory studies included a cholesterol of 80 mg% and an albumin of 2.1 gm/L with normal globulins. The calcium was 6.0 mg%; phosphorus 2.4 mg%; magnesium, 1.1 mg%; alkaline phosphatase, 225 IU; serum iron, 24 μg%; and the iron-binding capacity, 222 μg%. Triolein and I^{131} oleic acid absorption were 2.2% and 1.5% respectively. The d-xylose absorption was 1.8% and the carotene 20 μg%.

The hemoglobulin was 8.9 mg%; the hematocrit, 29%; and the WBC, 12,200/mm^3 with a normal differential. Platelets were 400,000/mm^3 and a bone marrow aspirate was within normal limits. A sigmoidoscopy and barium enema were normal. An upper gastrointestinal series revealed marked irregularity of the jejunum and ileum with thumb-printing, nodularity, and thickening of the folds (Fig. 1). There was also segmentation and flocculation of the barium in the small bowel. Peroral jejunal biopsy was negative but an exploratory laporatomy showed metastatic melanoma. The patient was treated with several chemotherapeutic agents and expired shortly afterwards.

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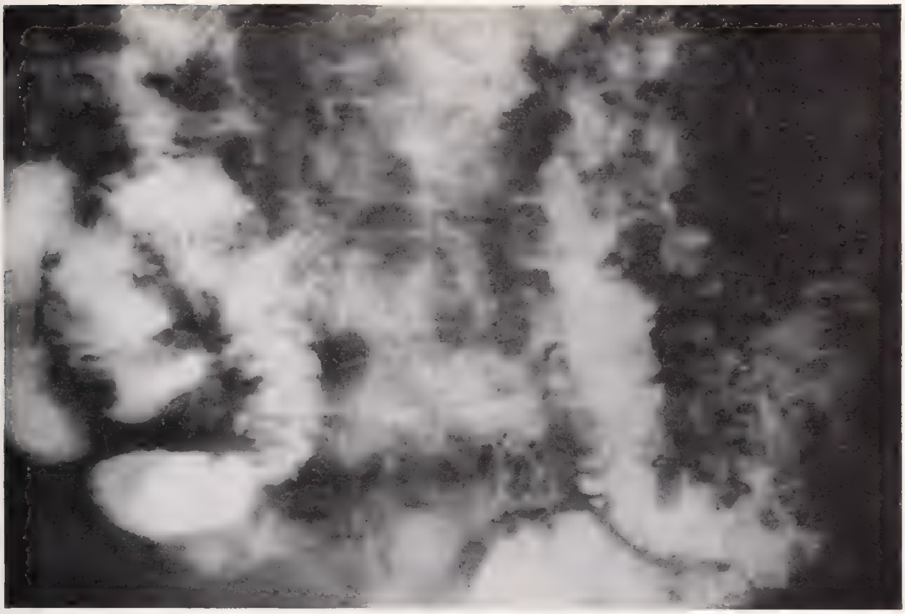

FIG. 1. Roentgengram showing prominent nodularity and thickening of the bowel wall.

Necropsy revealed extensive replacement of the small bowel by metastatic melanoma (Fig. 2). The tumor nodules were scattered throughout the entire length of the small bowel replacing approximately 70% of its surface area. The tumor deposits were ulcerated and covered with colonies of gram negative rods. The remaining mucosa was normal and the lymphatics in both the bowel wall and mesenteric nodes revealed neither tumor nor obstruction. Metastatic melanoma was also present in the gallbladder and hilar and submandibular lymph nodes. The lungs showed multiple recent pulmonary thrombo-emboli.

Discussion

Malignant melanoma is an aggressive tumor in which widespread metastases are common. Involvement of the small bowel occurs in approximately 1 percent of cases and may produce a varied symptomatology (1, 2). Malabsorption, however, has never to our knowledge been documented to result from intestinal involvement by either metastatic melanoma or any infiltrative neoplastic process other than those of the lympho-reticular system. The development of malabsorption in lymphomatous infiltration of the small bowel is a well known phenomenon, although the mechanisms by which it occurs are still unclear (3). Obstruction of lymphatics by lymphoma has been emphasized by some authors while others consider mucosal alterations as the primary event (4, 5). Malabsorption has also been described to occur with neoplasms remote from the gastrointestinal tract. This observation suggests the existence of a tumor elaborated humoral factor capable of altering the intestinal epithelium (6). Primary gastrointestinal carcinomas have been noted to occur in association with steatorrhea as well, however, they appeared to be a complication of rather than a cause for malabsorption (7).

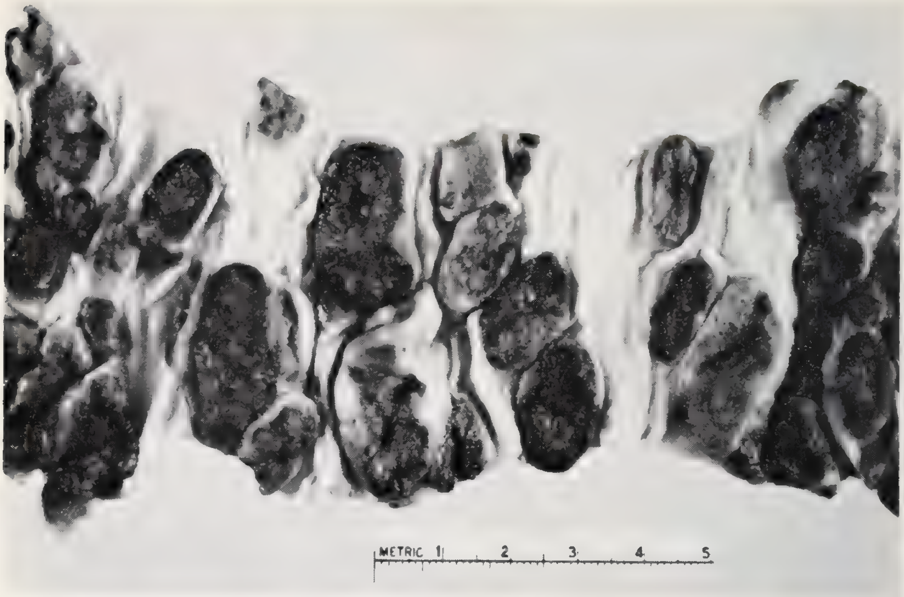

FIG. 2. Segment of jejunum showing extensive involvement by metastatic melanoma. Note diffuse ulceration of tumor nodules.

Examination of the present case revealed replacement of approximately 70 percent of the small intestinal mucosa by metastatic melanoma. The tumor nodules were uniformly distributed throughout the small bowel. Their surface was ulcerated and showed overgrowth by gram negative rods. The intervening mucosa was normal and the lymphatics in both the bowel and mesenteric nodes showed no evidence of obstruction or tumor.

Two factors appear to be important in the pathogenesis of the malabsorption observed in this case. The extensive replacement of the small intestinal mucosa by tumor must have limited the absorption of all food materials significantly. Secondly, the bacterial overgrowth present on the surface of the tumor nodules may have resulted in a process comparable to the blind loop syndrome, with deconjugation of bile salts and resultant inhibition of fat absorption. Bacterial utilization of carbohydrate may also have been a factor.

Malabsorption is a symptom of many diverse disease states often requiring an exhaustive search for its cause. The present case illustrates still another entity responsible for its development, namely the extensive involvement of the small bowel by metastatic carcinoma.

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A Study of Spinal Fluid Homovanillic Acid (HVA) in Patients with Diseases of the Nervous System

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Introduction

The early diagnosis of Parkinson's Disease by means of an objective biochemical test is now important because of the development of Levodopa as treatment for this illness. It is also necessary at times to predict the type of response an individual patient may have to L-dopa therapy. At present, no diagnostic test is available for Parkinson's Disease and the diagnosis is usually made by clinical examination.

Since the work of Ehringer and Hornykiewicz (1), it has been known that the dopamine concentration in the basal ganglia of patients with Parkinson's Disease is low. This information led directly to the use of L-dopa to treat patients with Parkinson's Disease and, in all studies, has helped at least 50% of the patients for a period of two to three years (2–6).

It was first shown by Anden (7) in 1963 that HVA is present in the spinal fluid of man and animals. A rough correlation has been made between the concentration of dopamine and homovanillic acid in the basal ganglia of animals and the concentration of HVA in the spinal fluid (8). For this reason, studies have been made by a number of investigators of the HVA concentration in the spinal fluid in patients with various neurologic diseases (9–15).

Methods

In this study, 120 spinal fluids have been analyzed for concentration of HVA. The patients studied were all neurologic patients admitted to either The Mount Sinai Hospital in New York City or the Bronx Veteran's Administration Hospital. The patients were examined by neurologists and classified into four categories of disease. These classifications were made before knowledge of the HVA levels were obtainable and before response to L-dopa therapy was established in the individual patients.

A. Typical Parkinson's disease patients.

B. Patients with basal ganglia disease and who have akinesia and rigidity but do not fit into the general classification of Parkinson's disease, because of the appearance of certain phenomena not usually seen in Parkinsonism. These include chorea or dystonic movements, dementia, dysarthria, dysphagia, or eye movement abnormalities out of proportion to extrapyramidal dysfunction. Some patients in this category might be classified as progressive bulbar palsy (Steele-Richardson-Olszewski syndrome) (16) or Creutzfeld-Jacob syndrome.

C. A small group of patients with spontaneous chorea or dystonia.

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D. Twenty-five patients who had other diseases of the nervous system and had no evidence of basal ganglia dysfunction.

The patients were all hospitalized and spinal fluids were studied after routine lumbar puncture was performed. The first 5–10 cc's of spinal fluid was frozen and later analyzed as described below. There were no restrictions put on the time of the spinal tap, nor was there any dietary control. These patients were frequently taking anticholinergic drugs at the time of the spinal tap.

Method of HVA determination

HVA was measured by the modification of Gerbode (17) and Bowers of the method of Anden et al (7). A 2 ml sample of CSF was analysed, and the spectrum of the fluoriphore recorded using a Hitachi fluorescence spectrometer. Samples which did not demonstrate a discrete fluorescence peak at 420 millimicrons, or which had high blank values were rejected.

Results

The results of the spinal fluid determination of HVA is summarized in Figures 1 to 4. Figure 1 shows the HVA concentration in the patients who were not on L-dopa therapy. The four groups, A, B, C, and D, have been described above. Patients with Parkinsonism had an average level of 9.4 ng/ml of HVA with a standard deviation of 6.8 ng/ml. All patients in this group had a concentration below 20 ng/ml except for one patient with a level of 36 ng/ml. This patient was a 44-year-old man with severe akinesia, poor fine movements, and abnormal handwriting. No tremor was noted, but he was considered to be typical of Parkinson's disease. It is of interest to note that this patient was unresponsive to L-dopa therapy at levels of 6 gms per day for six months and he did not respond to treatments of L-dopa plus MK-486, a dopa decarboxylase inhibitor (alpha methyl dopa hydrazine*). The patient did not develop dyskinesias, which is usually characteristic of Parkinson patients when on the L-dopa/MK-486 combination.

Patients in categories B, C, and D had mean HVA concentrations of 17.5, 17.5, and 20 ng/ml respectively (Fig. 1). One can conclude that the Parkinson patients have low HVA levels in the spinal fluid; however, it is not a diagnostic test as some of the patients in the other categories had HVA levels below 20 ng/ml.

Figure 2 is an attempt to compare the response of individual patients to L-dopa therapy with spinal fluid levels of HVA. Two groups of patients are noted here: 1.) The Parkinson's disease group (Group A of Figure 1), and 2.) Basal ganglia disease (non-Parkinson) (Group B and D of Figure 1). Most patients without Parkinsonism did not respond to L-dopa therapy. In all groups, patients with low HVA levels in the CSF tended to have a greater responsiveness to L-dopa than did the patients with higher HVA levels. No patient with an HVA level above 14 ng/ml responded to L-dopa therapy. The

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* Merck, Sharp, and Dohme.

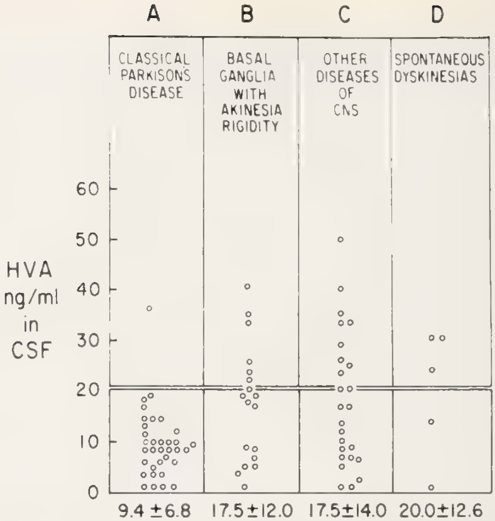

FIG. 1. The concentration of HVA in the lumbar spinal fluid is shown for each patient before starting on L-dopa therapy. The four clinical categories of neurological diseases are described in text. The value below the line represents the mean with one standard deviation.

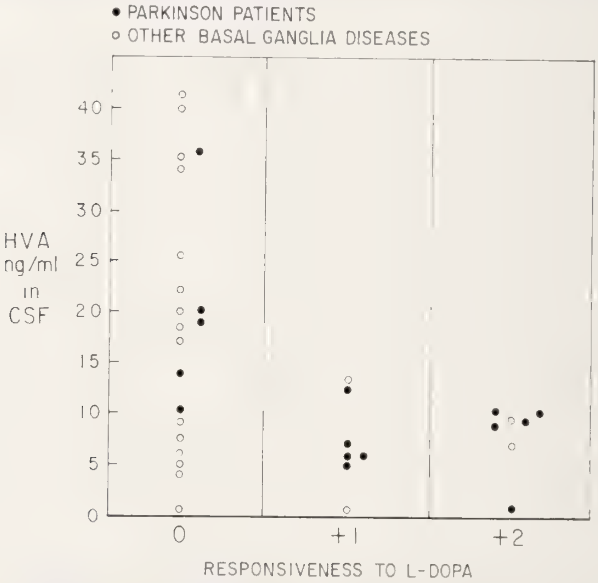

FIG. 2. Both Parkinson's disease of patients (Group A of Figure 1) and non-Parkinson's disease patients (Group B and D of Figure 1) were treated with L-dopa. The response to L-dopa is correlated in this Figure to the initial HVA level in spinal fluid before treatment with L-dopa. The patients with HVA levels over 15 ngs./ml. do not respond as well to L-dopa as those patients with HVA levels below 15 ngs./ml. (see text).

few non-Parkinson patients who had some therapeutic response to L-dopa were those with low HVA levels.

Figure 3 shows the HVA level in the spinal fluid of patients receiving L-dopa or receiving L-dopa plus MK-486. A large spread is noted among these patients

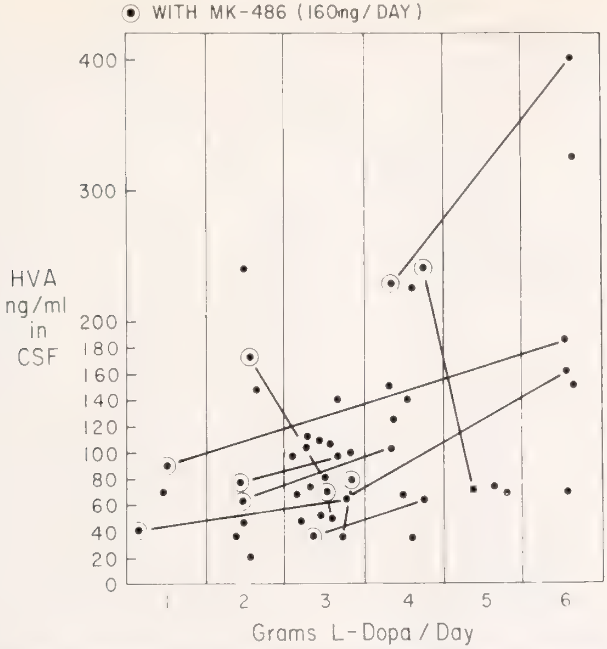

FIG. 3. This Figure attempts to correlate the HVA level in the lumbar spinal fluid to the amounts of L-dopa ingested by the patient. The patients studied in the graph were from Groups A and B, although most of the patients were Group A of Fig. 1 (Parkinson's disease). All patients were on the L-dopa dosage at least four weeks. The lines joining dots represent the same patient who had spinal taps before and after the addition of a dopa decarboxylase inhibitor—MK-486 (Merck, Sharp & Dohme) (alpha methyl dopa hydrazine (see text).

with levels ranging between 30 ng/ml to a maximum of 400 ng/ml. No correlation is possible between the amount of L-dopa given in a patient and the height of the HVA level. The circle-dots are patients who were receiving MK-486 with L-dopa at the time of the spinal tap. No significant difference is noted in the level of HVA during MK-486, although there appeared to be a tendency toward an increase in the HVA level when patients are on MK-486. No correlation was possible between the clinical response of the patient and the height of the HVA in the spinal fluid.

Figure 4 analyzes the production of dyskinesias in patients on L-dopa or MK-486 plus L-dopa. Note that a large number of patients with spinal fluid HVA levels above 100 ng/ml did not have dyskinesias. The patients on MK-486 plus L-dopa have a high incidence of dyskinesias with relatively low HVA levels. The three patients who were not on MK-486 and developed dyskinesias during the spinal tap period had HVA levels in the spinal fluid above 120 ng/ml.

Discussion

A number of investigators in the past have analyzed the HVA level in the spinal fluid of patients with various neurologic diseases (8–15). Our results are similar to these investigators and confirm the findings that patients with Parkinsonism have low HVA levels. Although we were not able to obtain ventricu-

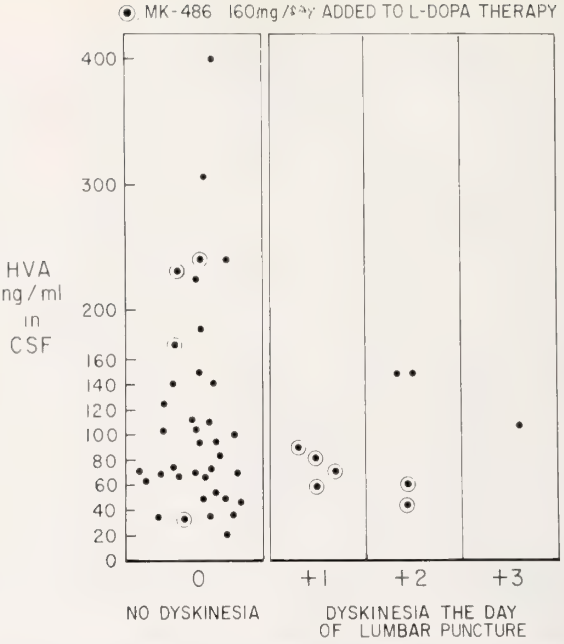

Fig. 4. This Figure is an attempt to correlate the production of L-dopa induced dyskinesias to the value of HVA in the lumbar spinal fluid. The patients on MK-486/L-dopa combination have a high incidence of dyskinesias although the HVA levels in the CSF in six cases are below 100 ngs./ml. Many patients with HVA levels above 150 ngs./ml. do not have dyskinesias.

The HVA level in the lumbar CSF is, therefore, not helpful in predicting the presence or absence of dyskinesias.

lar fluid from any of these patients, studies by Guldberg (18) and Papeschi (19) show that the concentration of HVA in the ventricular spinal fluid is in the range of 400 ng/ml in normal patients, whereas the Parkinson patients had an average level of 186 ng/ml. Bartholini (20) has shown that the HVA level in the spinal fluid is not derived from the circulating HVA in the blood. There is evidence that HVA in the spinal fluid is derived from brain metabolism via turnover of L-dopa to HVA, although some turnover is possible in capillary walls of the brain (21). Weiner (22), Sharpless (23), and Pullar (24) have shown that the concentration of HVA is increased when L-dopa is given orally. Pullar noted that DOPAC (dihydroxyphenylacetic acid) concentration is also increased when L-dopa is given. These investigators were unable to correlate the absolute rise of HVA in the spinal fluid with the clinical status of the patient.

Van Woert (25) noted evidence that patients with low HVA levels are more responsive to L-dopa than those with higher HVA levels. Our study confirms this finding in both the Parkinson patients and those patients who were not classified as Parkinson patients, but who, nevertheless, had a trial of L-dopa therapy. The use of probenecid may make this determination more meaningful (26–28).

The production of dyskinesias in patients on L-dopa is a common problem in the clinical care of Parkinson patients. Approximately 60 per cent of the patients develop dyskinesias during L-dopa therapy and in one-half of these patients the dyskinesias are the limiting factor in their response to the drug (29). The production of dyskinesias is, presumably, due to a large amount of L-dopa or dopamine in the striatum of these patients. One might expect, therefore, that the study of the spinal fluid would give some clue as to the cause of dyskinesias in individual patients. Figure 4, however, reveals that no correlation is possible between the height of the HVA level in the spinal fluid and the production of dyskinesias. Many patients did not have dyskinesias with high levels of HVA in the spinal fluid. Most patients who were taking the combination of MK-486/L-dopa had dyskinesias, although their HVA levels are at a generally low level (Fig. 4).

A number of diseases have been studied in regard to spinal fluid HVA levels. Dencker (9) studied patients with depression and mania and was unable to correlate any clinical phenomena with the HVA levels. Gottfries (10) studied patients with senile dementia, Parkinsonism, and presenile dementia, and did not find any clear adnormality except for the fact that the Parkinson patients had low HVA levels in the spinal fluid. Brody, Chase, and Gordon (30) noted in a recent article that there were low HVA levels in spinal fluids of patients with Parkinson dementia and in patients with amyotrophic lateral sclerosis in Guam. Mendell (15) noted a reduction of HVA levels in patients with classical amyotrophic lateral sclerosis.

Information is still not available on the following diseases which are related on descriptive grounds to Parkinson's disease—progressive bulbar palsy; Creutzfeld-Jacob syndrome; and Shy-Drager syndrome (31).

Conclusion

The HVA concentrations in the spinal fluid of patients with neurologic diseases have been determined. The patients with Parkinson's disease have a lower level of HVA, but this is not diagnostic in individual cases. A low HVA level in a patient before starting L-dopa therapy implies that a response to L-dopa is likely. The concentration of HVA in the spinal fluid during L-dopa therapy or MK-486/L-dopa therapy is not correlated with the improvement in the patient or in the production of dyskinesias.

Acknowledgment

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Reminiscences of Fifty Years in Cardiology at Mount Sinai with Special Reference to the Two-Step Test

ARTHUR M. MASTER, M.D.

The reminiscences which follow span almost in its entirety the history of clinical electrocardiography. Dr. Arthur Master, a giant in the field, became involved while still a medical student and has remained productive over the ensuing fifty years. The Two-Step Test, which is extensively reported on is indelibly connected with his name. Modestly, Dr. Master, does not mention his classic paper on "Fatty Degeneration of the Heart" which administered a deserved "coup de grace" to that diagnostic aberration of bygone days. No apology is made for the anecdotal nature of this paper because of the importance of preserving its content for the history of cardiology. *Editor's note.*

Dr. B. S. Oppenheimer, then an attending physician of The Mount Sinai Hospital had heard of my interest in cardiology and electrocardiography from Dr. Harold E. B. Pardee of the Cornell University Medical College, with whom I had done some volunteer work while still a student. At Dr. Oppenheimer's invitation early in 1920, I spent two afternoons a week in the cardiographic department of The Mount Sinai Hospital (this was during my last year at Cornell), so I really became associated with Mount Sinai, New York in 1920.

The huge, heavy electromagnet is illustrated in Figure 1. All this equipment was in the electrocardiograph room of The Mount Sinai Hospital in 1920. The machine was indeed a huge affair, primarily because of the long optical system; long brass tubes contained the lenses. The electric current produced by the contraction of the heart passed through a gilded hairline quartz string which was suspended between the two poles of the large powerful electromagnet (Fig. 1). The heart current produced lines of force circumferentially around the string, and, these, in turn, interacted with the lines of force running from the south to the north between the poles of the powerful electromagnet. The interaction of these lines of force resulted in the human electrocardiogram. The optimal system simply magnified the movements of the human ECG on the photographic plate. An arc lamp was the source of light and continuously sputtered out. Photographic plates, not film, were used to record heart beat.*

Back in 1920 the ECG department was located in a room behind Ward C, a male medical ward. When an ECG was to be taken, a technician had to trundle a large cart to the ward. On the cart were three-inch wide gauze bandages soaking in brine-filled jars and a heavy electric cable, hundreds of feet long so that it could reach every bed on the ward and even the beds in the rooms behind the ward. One end of the electric cable was plugged into an electric wall socket and then the ECG was transmitted to the ECG department. To take the

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* Just compare this machine with the current small compact units, weighing about 16 to 22 pounds, which you have in your office or transport in the back of your car. New machines, weighing only 3 pounds, are now being described.

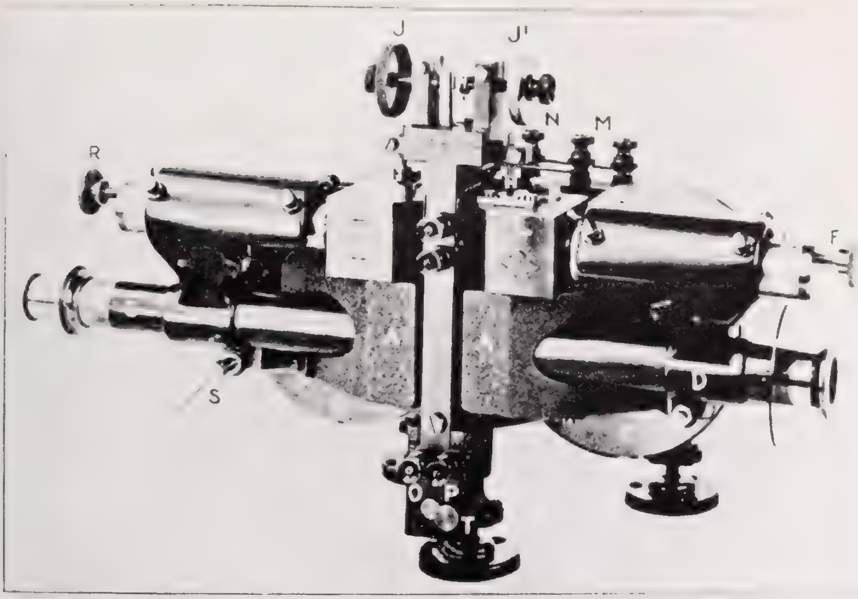


FIG. 1. The north and south poles of the electromagnet are marked A, A. The string is suported between these two poles but not seen in the picture. The light from an arc lamp is sent through the optical pieces C and D which focus on the hidden string and illuminates it. One is the ocular portion and the other the objective. The latter would project the movement of the string into the camera which also is not shown. (*The Mechanism and Graphic Registration of the Heart Beat*, Sir Thomas Lewis, 3rd ed., Shaw & Sons, Ltd., London 1925, p. 31.)

ECG, zinc electrodes were placed on the two forearms and the left leg of the patient and the dripping wet, saline-soaked bandages were then wrapped around them. Large pieces of oilcloth were placed under the limbs to protect the bed from being soaked. The ECG technician was not very popular with the nurses of the hospital, and you can readily understand why. The bed linen and even the mattresses were often soaked through.

Once the zinc electrodes were in place, they were connected to the cable wires, and the ECG was ready to be recorded. At this point, it was necessary for the technician to go to the nurse's desk and wait patiently until she could use the phone to tell the waiting technician in the ECG department to proceed and take the tracing.

If the patient was ambulatory he was brought to the ECG department, either walking or in a chair. At that time we had the patient sit in an Adirondack chair (Fig. 2) while his tracing was recorded. This chair was extremely comfortable; the patient was completely relaxed and there was indeed a minimum of muscle tremor. Use of this chair was discontinued when the American Heart Association, in its wisdom, decreed that in order to standardize the ECG procedure and to make records comparable, all ECG's should be taken with the patient in the recumbent position.

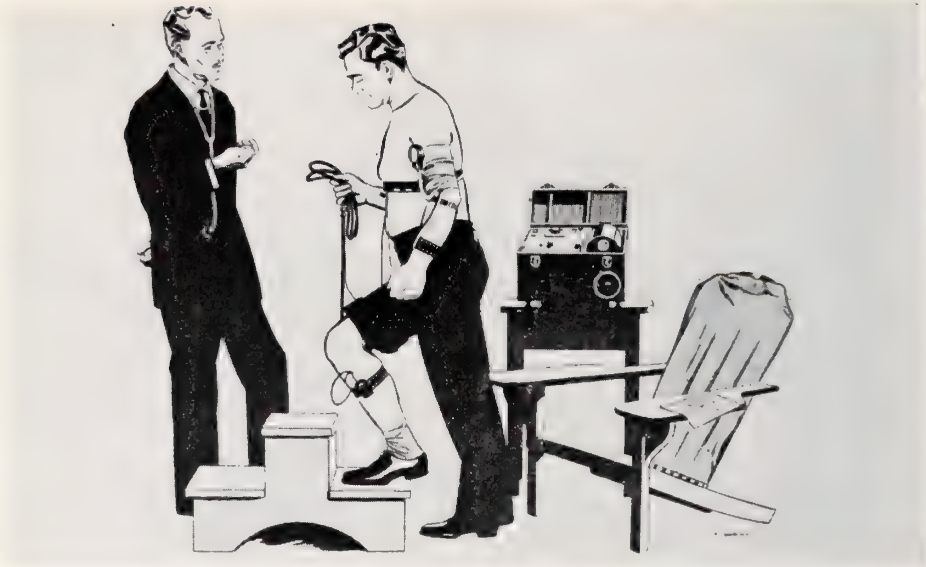


FIG. 2. Shows standard "2-steps" each 9 inches high, an electrocardiograph machine with "instomatic" action, Adirondack chair with wide arms, technician or physician with stop watch in hand, person to be tested with electrodes strapped on and blood pressure cuff and gauge bound around arm.

Figure 3 shows a patient sitting in a chair with his hands and left foot in three separate clay jars filled with saline solution. Each jar contains a zinc electrode and a wire attached to each electrode leads into the gilded quartz string suspended between the north and south poles of the powerful electromagnet. Thus leads I, II and III were recorded from the limb leads.

At the time that I am referring to, beginning in 1920, Dr. Hubert Mann, a physician with a degree in electrical engineering, was a member of the cardiographic department at The Mount Sinai Hospital, New York. Mathematically, he worked out the "monocardiogram." This is the vectorcardiogram of today which has been applied universally.

I was responsible for at least two innovations in the electrocardiographic technique and possibly a third. Years ago when an ECG was about to be recorded, it was necessary either to dim the overhead light in the room or to turn it off entirely otherwise the light rays would enter the photographic plate as the tracing was being recorded. I had Mr. Phillips, our engineer, make a cover of tin metal which projected out over the ocular lens. With this protection, all the lights in the room could be kept on. The companies that manufactured the ECG machines immediately incorporated this improvement in all their models both stationary and portable. Did I receive royalties? It never entered my mind!

In order to facilitate communication between the technician in the ward and the technician in the ECG department, I had these two use earphones and chest pieces similar to the ones used by telephone opertors. Thus they could speak

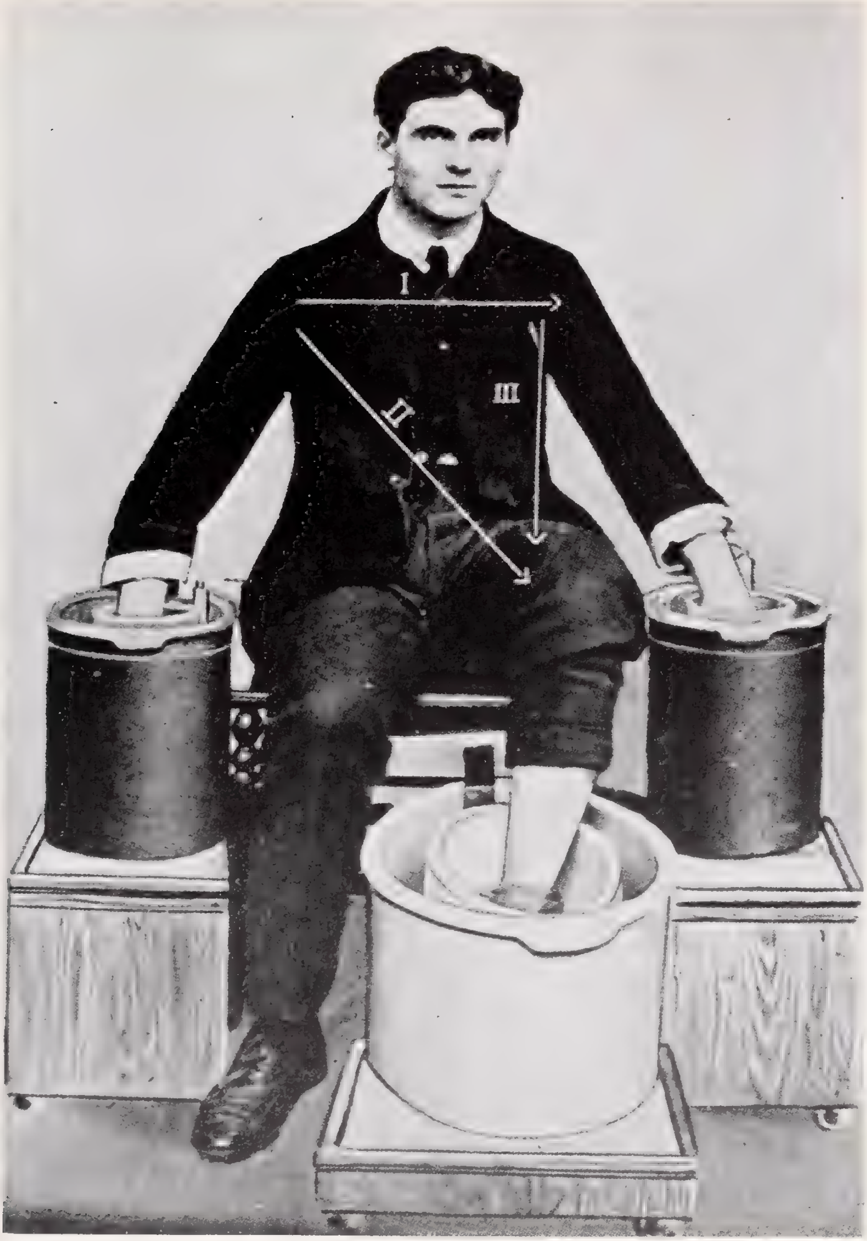


Fig. 3. This shows a patient sitting in a chair with his hands and left foot in three separate clay jars filled with saline solution. Each jar contains a zinc electrode and a wire attached to each electrode leads into the gilded quartz string suspended between the north and south poles of the electromagnet. Thus leads I, II and III were recorded from the limb leads. (*The Mechanism and Graphic Registration of the Heart Beat*, Sir Thomas Lewis, 3rd ed., Shaw & Sons, Ltd. London 1925, p. 46.)

directly to each other at any time, through the cables and wires in the walls, without using the hospital phones.

A change that had the greatest influence on all electrocardiography was the "direct writer" electrocardiograph machine. Three German refugees had constructed a direct writing machine. They looked me up at Mount Sinai in 1946, just after I had returned from World War II and they told me they were anxious to put it on the market. Would I please help them? In order to test its accuracy, we took ECG's in succession on 300 patients. We found that every single tracing taken on the direct writing machine was duplicated by our large accurate hospital machine. Regardless of the contour of the tracing, the heart rate or the arrhythmia, the direct writing machine faithfully reproduced the ECG. Of course, these poor refugees, one a scientist, one a physicist and one a salesman needed financial backing in order to promote their machine. Hence, I notified the two outstanding manufacturers of electrocardiograph machines that a high-precision direct writing machine had been made and that it was accurate, hardy and serviceable. Neither company evinced any apparent interest in this fact, but each quietly bought a machine for $300 from the refugees. Since nothing on the machine was patentable, they then constructed the direct writer themselves! They were able to do this legally, but morally it was a crime. To make matters worse, the president of one of these companies openly boasted at heart meetings how he had put one over on these refugees. The latter, of course, went broke after spending two years and all their capital in constructing the direct writer electrocardiograph machine. Many, many thousands of direct writer ECG machines have been produced since then.

Evolution of the Two-Step Exercise Test

For years doctors had had their patients perform exercise tests to determine the heart's function; dumbbells, hopping 20 to 40 times on each foot, raising the hands above the head up and down, or pushing them forward, bending at or stooping at the knees, bending the trunk and touching the toes, and countless other body movements were utilized. Not a single exercise was standardized for age, sex, weight, or height. A child of nine, a person of 19 or 29, a man or woman of 59 years of age would be given the same 5- or 10-pound dumbbells and all would be asked to perform the same number and type of movements. The English physiologist, Enid Tribe Oppenheimer, and I thought that this was wrong. We were acutely aware of the need for standardization and so we began to evolve a test taking into consideration the patient's age, sex, weight and height. We made an assay of all kinds of permutations and combinations of steps in regard to the time of the walk and the height of the steps. We finally decided on two steps, each nine inches high, the walks up and down performed in one and a half minutes time exactly. This one and a half minutes was chosen as it made foot-pounds performed per minute easily calculable on a one and a half-foot height walk. Multiplying the number of trips performed by the patient's weight gave the number of foot-pounds of work per minute. (In the late thirties the time was changed to 3 minutes as we found, empirically, that this time unit with double the number of trips gave more precise results.) I should have said that until 1934 when I was asked to take charge of the cardiographic department of The Mount Sinai Hospital, I split my time between this institution and Cornell University Medical College. Hence, although the early formulation of the two-step was done at Cornell University Medical College, our controls (faculty) came equally from The Mount Sinai Hospital and Cornell. In fact, Dr. Enid Oppenheimer was a volunteer worker at Mount Sinai.

We recorded the age, sex, weight and height of each examinee. We determined the maximum number of trips he or she could perform in one and a half minutes with his blood pressure and pulse rate returning to the resting levels within two minutes of cessation of the test. We turned our data over to Dr. Eugene Smith, Professor of Mathematics at Columbia University, and asked him to construct a table of trips for us. You may wonder why we did not turn our data over to the Science Department of Cornell University. The Mount Sinai Hospital had no scientists and so proximity is the answer—the mathematics and physics departments of Cornell were in Ithaca, New York. Dr. Smith was very cooperative. We had one of his associate mathematicians develop the table (1, 2).

The mathematicians discovered that in climbing steps nine inches high the height of the patient did not matter; there was no mechanical advantage to the taller person. Empirically, with time, we found that the 3 minute exercise test and doubling the number of climbs was more suitable. The final table (Table I), shows the number of trips related to age, sex and weight. Those for women are given in parentheses and appear alongside the numbers for men. As one grows older, the number of required trips is less, and as one gains weight, the number of trips one can perform is also less, that is, the heavier the patient, the

TABLE I

Trips Performed In Master Double (3 minute) Two-Step Exercise Test Males and Females*

Weight	Age In Years												
	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79
lb.													
50-59	64(64)												
60-69	62(60)												
70-79	60(58)												
80-89	58(56)	58(56)	58(56)	56(54)	54(52)	54(48)	52(46)	50(44)	50(42)	48(42)	46(40)	46(38)	44(36)
90-99	56(52)	56(54)	56(52)	54(50)	54(48)	52(46)	50(44)	50(44)	48(42)	46(40)	44(38)	44(38)	42(36)
100-109	54(50)	56(52)	56(52)	54(50)	52(48)	50(46)	50(44)	48(42)	46(40)	44(38)	44(36)	42(36)	40(34)
110-119	52(46)	54(50)	54(50)	52(48)	50(46)	50(44)	48(42)	46(40)	46(38)	44(36)	42(36)	42(34)	40(32)
120-129	50(44)	52(48)	54(48)	52(46)	50(44)	48(42)	46(40)	46(38)	44(38)	42(36)	40(34)	40(32)	38(30)
130-139	48(40)	50(46)	52(46)	50(44)	48(42)	46(40)	46(38)	44(38)	42(36)	40(34)	40(32)	38(30)	36(30)
140-149	46(38)	48(44)	50(44)	48(42)	48(40)	46(38)	44(38)	42(36)	40(34)	40(32)	38(32)	36(30)	36(28)
150-159	44(34)	48(42)	50(40)	46(40)	46(38)	44(38)	42(36)	40(34)	40(32)	38(32)	36(30)	36(28)	34(26)
160-169	42(32)	46(40)	48(38)	46(38)	44(36)	44(36)	42(34)	40(32)	38(32)	36(30)	36(28)	34(26)	34(24)
170-179	40(28)	44(38)	46(36)	46(36)	44(34)	42(34)	40(32)	38(32)	36(30)	36(28)	34(26)	34(26)	32(24)
180-189	38(26)	42(36)	46(34)	44(34)	42(34)	40(32)	38(32)	38(30)	36(28)	34(28)	32(26)	32(24)	30(22)
190-199	36(24)	40(34)	44(32)	42(32)	42(32)	40(30)	38(30)	36(28)	34(26)	32(26)	30(24)	30(24)	28(22)
200-209		38(32)	42(30)	42(30)	40(30)	38(28)	36(28)	34(26)	32(26)	32(24)	30(22)	28(22)	28(20)
210-219		36(30)	42(28)	40(28)	38(28)	36(26)	34(26)	34(26)	32(24)	30(22)	28(22)	28(22)	26(20)
220-229		34(28)	40(26)	40(26)	38(26)	36(26)	34(24)	32(24)	30(22)	28(22)	26(20)	26(20)	24(18)

* Master, A.M. & Rosenfeld, I.: The "Two-Step" Exercise Test Brought Up to Date. New York J. Med. 61:1850 (June 1) 1961.

less efficient is the heart. This tale indicates the number of trips to be performed in three minutes from 15 through 79 years of age.

We made some interesting observations when we were still using blood pressure and pulse rate responses as criteria to the two-step test. We found that cardiac efficiency (foot-pounds per minute) was related to age, sex, and weight of the patient. At approximately 24 to 30 years of age a man performed the maximum number of foot-pounds, 3,700 foot-pounds per minute, and a woman performed the maximum of 3,100 foot-pounds per minute at about 22 to 30 years of age. After these ages, cardiac efficiency declined, that is, the patient could no longer perform as many trips (more accurately, foot pounds of work per minute) and have his blood pressure and pulse rate return to resting levels within two minutes of completion of the two-step exercise test. We also found that adult women are not as efficient as adult men and therefore they are asked to perform fewer trips on the test.

In Figures 4A & 4B are shown the curves (men and women) relating foot-pounds per minute, or the efficiency of the heart to age and weight. The optimum weight for maximum heart efficiency was 155 to 170 pounds in a man and about 135 pounds in a woman. If heavier than this, the heart was less efficient. In other words, the efficiency of the heart decreased as the patient's weight increased.

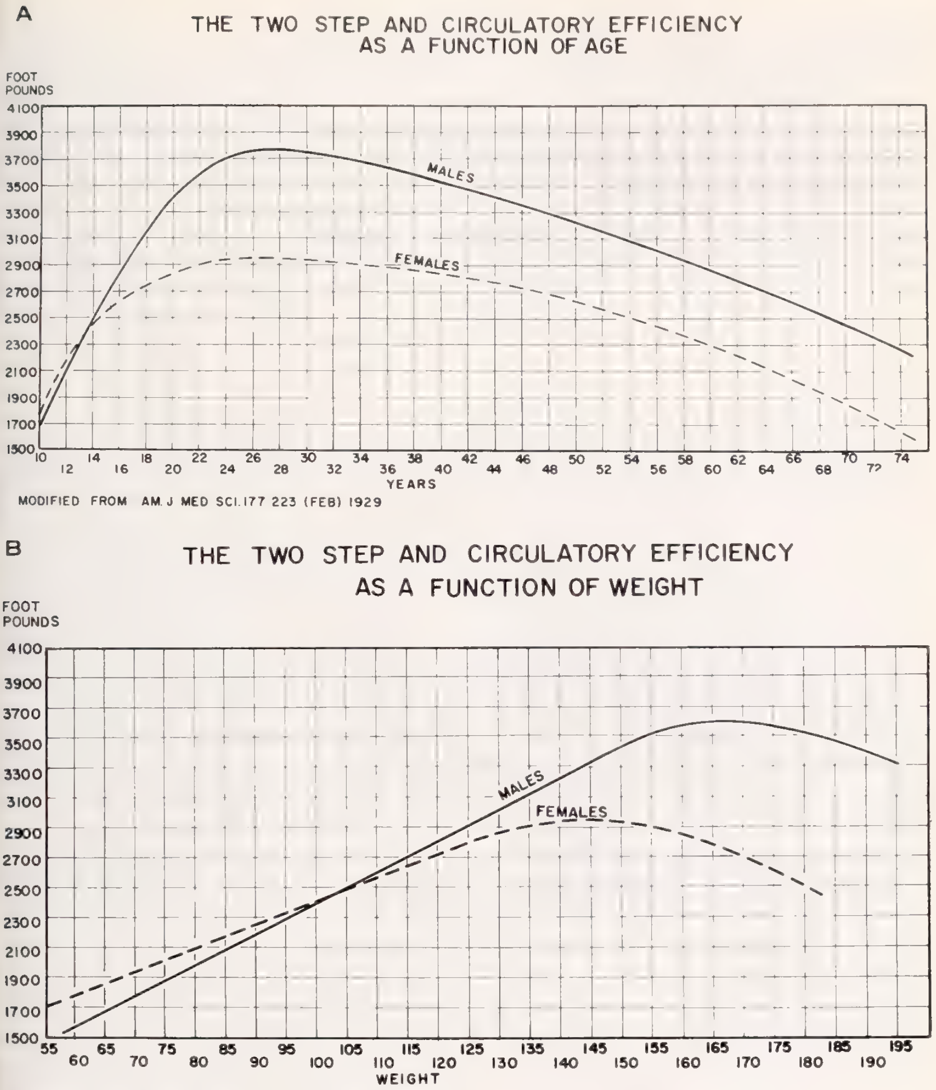
Years later, in the late thirties, because the blood pressure and pulse rate were so labile, we began using the ECGs; they were much more stable and did not vary with emotion or excitement. Empirically, we found the ECG more practical than the blood pressure and heart readings, and empirically we observed that a three minute exercise with double the number of trips gave us more reliable results than a minute and a half walk on the steps with half the number of trips.

Historical Background of Exercise Electrocardiograms

An early electrocardiogram taken by Einthoven with the patient at rest and one taken by him after the patient ran up a flight of stairs is shown in Figure 5. These were published by Einthoven in 1908 (3) and the latter probably represents the first exercise electrocardiogram recorded. Einthoven, however, made no clinical use of the effect of the exercise on the ECG.

In this country, Francis Wood, Mary Livesey and Charles Wolferth (4), all of Philadelphia, were the first to suggest recording the electrocardiogram after exercise to ascertain whether chest pain was cardiac or noncardiac in origin. However, they stated that this procedure could be dangerous and was only to be employed when the diagnosis was uncertain. This warning unfortunately discouraged would-be followers. Nevertheless, their suggestion was indeed a pioneer one.

Scherf in 1933 (5) began to work on exercise electrocardiography. As much as we were insistent on standardization of the exercise, he was unalterably opposed to it. He would have the patient repeat the effort that induced pain. We wondered what he would do if the patient experienced pain only during sexual



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Figs. 4A & 4B. These figures show the curves (men and women) relating foot-pounds of work per minute, or the efficiency of the heart, to age and weight. The optimum weight for maximum heart efficiency was 155 to 170 pounds in a man of 24 to 30 years and 135 pounds in a woman of 22 to 30 years of age. If heavier than these values and if older than these ages, the heart was less efficient. (Am J Med Sci 177:223, 1929.)

intercourse, or when he left his house in the morning, or when he awakened, or just as he went to the bathroom, or just as he opened the door of his house to the external world in the morning.

Katz and Landt (6) (Louis Katz, the father of our Arnold Katz) also had ideas on exercise electrocardiography. However, these authors did not standardize their exercise regimen for age, sex, weight and height; neither did Missal (7)

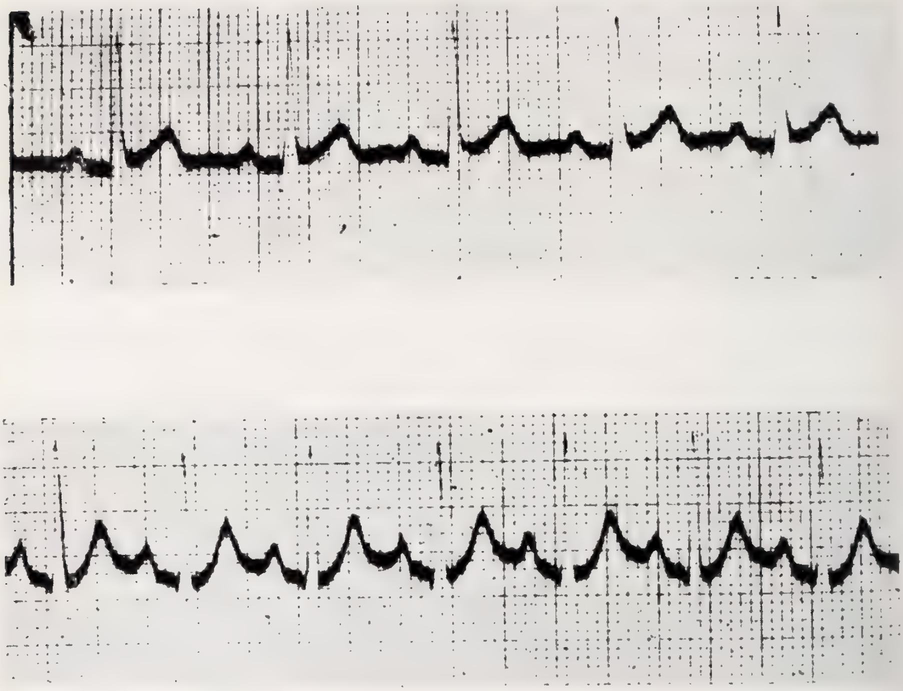

FIG. 5. The upper tracing shows lead II at rest. In the lower half, lead II is recorded after the patient ran up a flight of stairs. There was no abnormality; the heart rate was simply increased. (Einthoven, W.: Weiteres über Das Elektrokardiogram, Archiv für Physiologie 122:517, 1908.)

who actually suggested the use of our two steps. All these investigators usually asked the patient to perform the exercise or climb our steps until they were exhausted.

Another important dvance in electrocardiography occurred when the two-step test was "monitored," that is, recorded during the actual climbing up and down to the two steps. Dr. Isadore Rosenfeld and I found this procedure to be valuable in many ways, especially in detecting cardiac arrhythmias not discovered on physical examination or in the resting ECG and rarely not even in the post-exercise electrocardiogram (8, 9). By taking a resting ECG, then a monitored one during the performance of the two-step test and finally continuing into the usual post-exercise tracings, unsuspected arrhythmias would be discovered on one or more of these tracings and found to be the cause of the patient's unsteadiness, giddiness, pounding or palpitation of the heart, heart thump, irregular or "flutter" heart action, faint-like head sensations, and even syncope (10–18). Yet the physical examination and the resting electrocardiogram would disclose no cardiac irregularity. We first noticed this in 1942 and in numerous other reports but it is being rediscovered now that exercise will elicit arrhythmias not otherwise observed.

Present-Day Techniques

The main reason the patient can walk the steps steadily and we can record a good tracing during the exercise is that we now use the outer portions of the clavicles for positioning the leads. In this respect, we have followed Mason (19). These positions take the place of the left and right arm. The left leg electrode is placed just above the left iliac chest. A further improvement which makes a good recording possible is the disposable electrode. The small central shallow cup metal mesh is filled with electrode jelly or paste. Adhesive is attached around this metal center and is placed on the patient's skin and thus holds the electrode firmly and immovably in place.

Value of Standardization of the Two-Step Test

Figure 6 exemplifies the value of standardization of the test. This is the recording of a man with severe angina pectoris. You will note that his resting control ECG is normal. When we gave him iproniazid (Marsilid®), an adrenalytic and sympatholytic agent, he felt no pain at all, no matter what he did physically (20). In fact, the man often became inordinately active in a physical

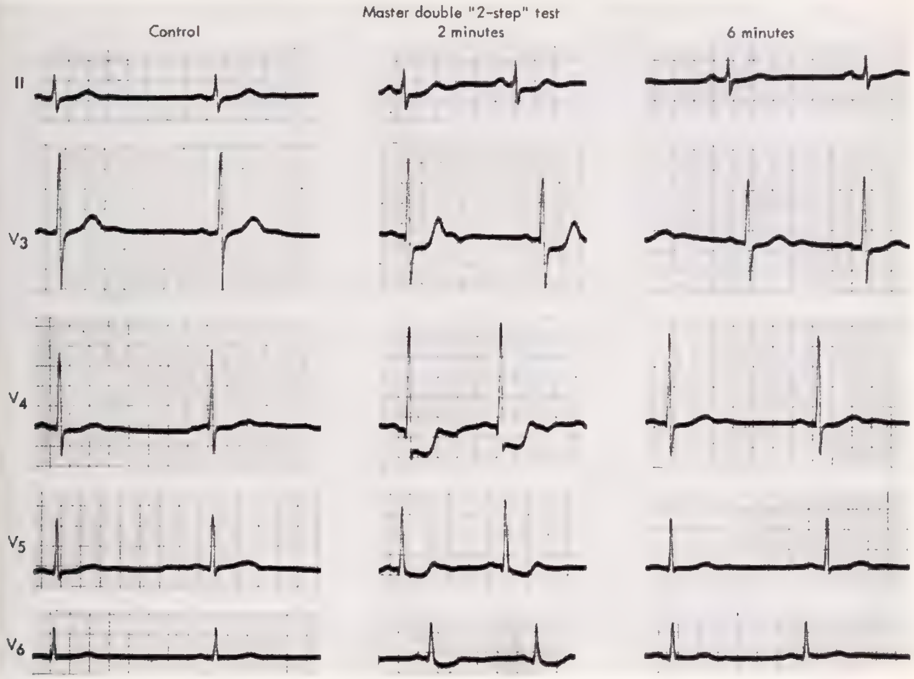

FIG. 6. This is a patient, H.K., male, aged 63 with angina pectoris. When he was placed on iproniazid (Marsilid®) he lost all his symptoms. Nevertheless, on the two-step exercise the test is very positive; the ST segment is dramatically depressed and the U-wave inverted. This is seen in the 2 minute tracing. Six minutes after exercise the tracing is back to the control configuration. (Dis Chest 51:347–383 (Apr.) 1967).

sense since the drug was also a psychic energizer. However, when he performed the two-step test, the S-T segment was dramatically depressed. In other words, despite complete relief from chest pain, there was no improvement in the underlying coronary disease. Paul Wood of England (21) obtained the same results with iproniazid, and we compared electrocardiograms. Thus, by standardizing the test, it can be performed anywhere in the world and the tracings are comparable. The two-step test can be employed for pharmacologic and physiologic studies as in the case we just cited.

I think that iproniazid was a remarkable drug, but it was taken off the market because of its supposed liver toxicity, specifically hepatitis. I never believed this nor did Dr. George Griffith, but our own Dr. Hans Popper, a world authority on liver disease, was of the opinion that the iproniazid was toxic to this organ.

Figure 7 also demonstrates the value of standardization of the two-step test.

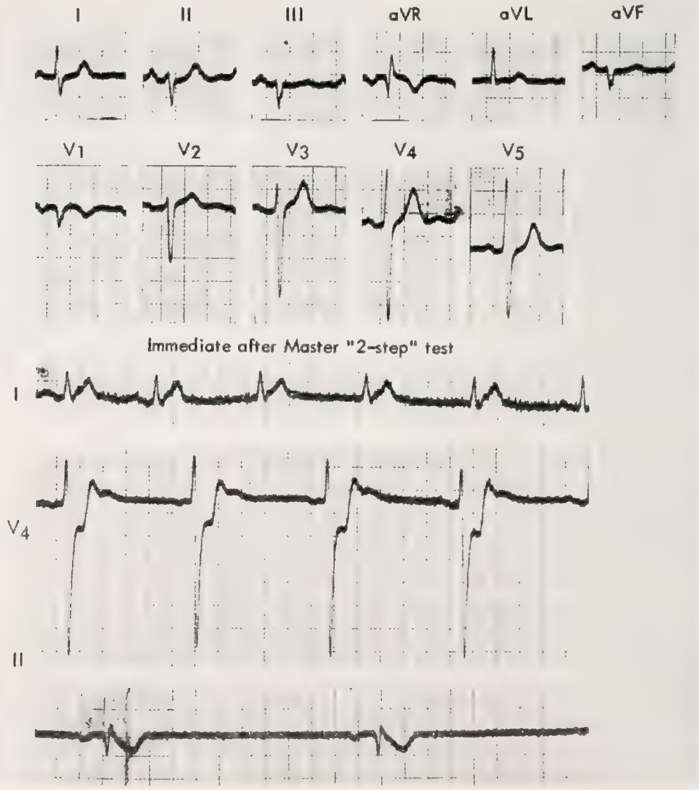

Fig. 7. This is a man, C.G., aged 69, with angina pectoris. The table called for 38 trips in 3 minutes. Instead of this limit, the family physician had the patient walk until the latter was exhausted. On the 58th trip the patient collapsed and went into convulsions. One can see the slowing heart rate in leads I, II and V4. The heart rate slowed 20-25 beats per minute. Fortunately, the patient recovered. (Master, A. M. and Rosenfeld, I.: Diagnostic Limitations of the Two-Step Test. In *Atherosclerotic Vascular Disease*, edited by A. N. Brest and J. A. Moyer, New York, Appleton Century-Crofts, 1967, pp. 309–320.)

These tracings were given to use by Dr. William Foley of New York Hospital. He obtained them from a physician who utilized the two-step test but with an improvement! It is almost an instinct to improve or innovate, and the physician in this case told the patient to walk until he was exhausted or until chest pain appeared. Our table called for 38 trips, but on the 58th trip you can see the startling slowing of the heart, a bradycardia down to 45, then down to 15 or 20 beats per minute. At this point, the man collapsed and suffered convulsions. Fortunately, he recovered. So standardization of the test makes for safety. The fact is that we have never had an accident. Of course, the test is never performed by a patient with an "impending" infarction or by a man who has had severe and/or prolonged chest pain within a week or two. Under these conditions, even a normal resting ECG is no indication for an immediate two-step test. We prefer to have the patient return in two weeks; if the tracing is still normal at that time, or if it was abnormal and there is no change, we will have him perform the test. Before he does so, however, there is the never-failing admonition which is given to every patient, to stop walking the very instant he experiences any chest sensation whatsoever.

Figure 8 shows the necessity of standardization by using the number of trips prescribed in the table. The tracing in this man was "monitored." The table

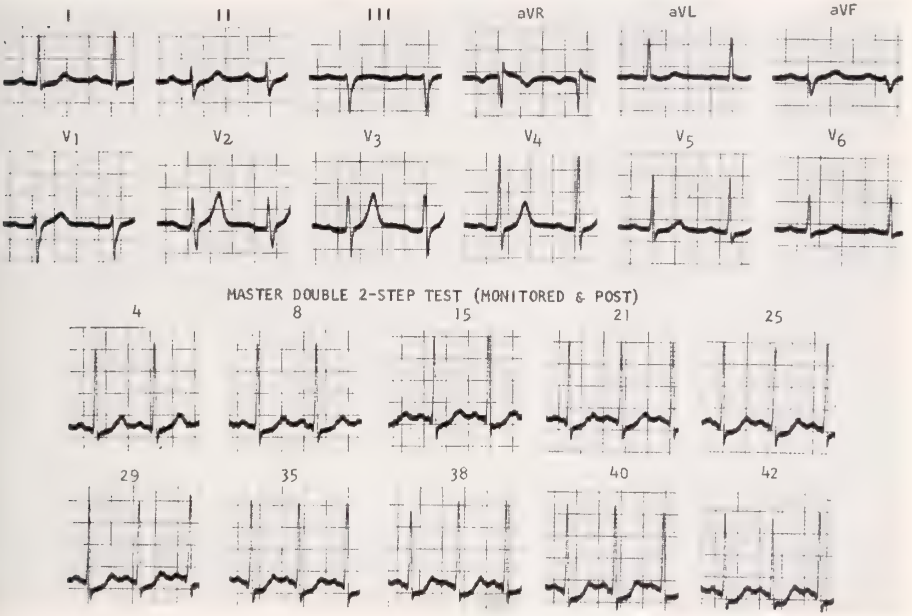

FIG. 8. This figure represents a man, J.F., aged 63, with angina pectoris. The upper two rows show an essentially normal 12-lead ECG. The exercise called for 42 trips and the lower two rows display the results of "monitoring" the patient as he walked over the two-steps. The electrocardiogram revealed ischemic depressions of the ST segment at the very last trip, namely the 42nd. Thus it was necessary to perform the full number of trips called for in the standardized table before the test became positive. (Dis Chest 51:347–383, 1967.)

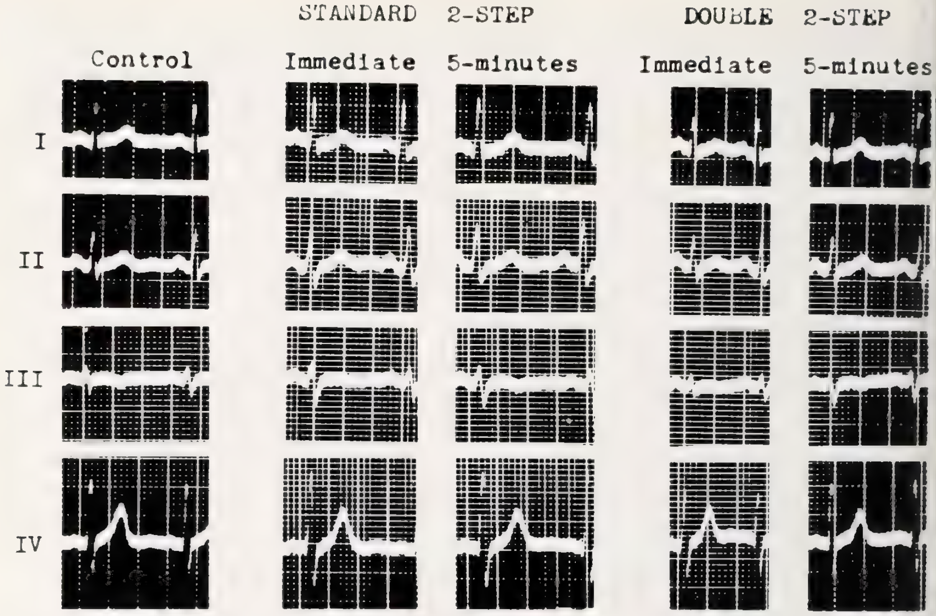

FIG. 9. J.C., male, 46, suffered two "heart attacks" for which he was given morphine and placed in bed for six weeks each time. The control 4 leads in the left column are normal. The middle two columns show the single two-step test, that is, half the number of trips walked in 1½ minutes. There was no change in the tracings. The last two columns represent the full 3 minute test but again the tracings were entirely negative. Further study disclosed the lesion from which the man had suffered, namely, a hiatus hernia. (Dis Chest 51:347–383 (Apr.) 1967).

called for 42 trips to be performed in the usual three minutes. Not until the 40th and 42nd trip did the electrocardiogram really disclose ischemic depressions in the S-T segment. It was necessary for this man to perform the full number of trips called for in the "standardized" table for the test to be positive.

Interpretation of Negative Test

Now that we have shown the value of an abnormal or positive two-step test, I wish to emphasize the importance of a negative test. A negative test virtually excludes coronary artery disease. This has been confirmed by us and the insurance companies (22–24).

A 46-year-old man had been a "cardiac cripple" for 20 years. He had suffered two attacks of severe chest pain for which he had had to have morphine, and for which he had been kept in bed for six weeks each time. We saw the patient at The Mount Sinai Hospital, New York. The control tracing was normal (Fig. 9).*

With the patient's history of two heart attacks, we initially had him perform a single test, that is, half the number of trips in one and a half minutes. There was no change in his ECG. The next morning the patient was asked to perform the full number of trips in the usual three minutes. You can see the control, the "immediate" and the "five-minute" tracings. Again, there was no alteration in the post-exercise electrocardiograms. In other words the test was negative.

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* Notice that we used leads I, II, III and the Wilson lead IV in the late thirties and very early forties for the two-step test. Notice also the thick line the galvanometer string left on the film. This was the type of electrocardiogram we obtained years ago.

We knew that a man who had had two severe transmural myocardial infarctions would, first of all, have had an abnormal resting control tracing and secondly, an abnormal two-step test, that is, positive test.

Further investigation revealed the lesion from which this man had suffered, namely, a hiatus hernia. This had been the cause of the patient's illness for years. The patient was reassured that he did not have heart disease and was told to return to work. He has been entirely well for years, merely giving his gastrointestinal tract exquisite care.

The two-step test can be performed for evaluating the adequacy of the coronary circulation in heart disease other than coronary artery involvement. It is easily employed in rheumatic or congenital heart disease.

An athletic 21-year-old man was eager to enlist in the army during the Korean War. However, the army would not accept him because of a loud grade III to IV systolic murmur heard over the pulmonary area (idiopathic dilatation of the pulmonary artery). The dilatation of the pulmonary artery was clearly demonstrable on x-ray.

We had him perform the two-step test; it was entirely negative (Fig. 10), substantiating good cardiac function and explaining the patient's lack of symptoms even after indulging in strenuous athletic sports. On the strength of the negative two-step test, he was accepted by the army. He did a three-year "hitch" and was in normal health when we last heard from him.

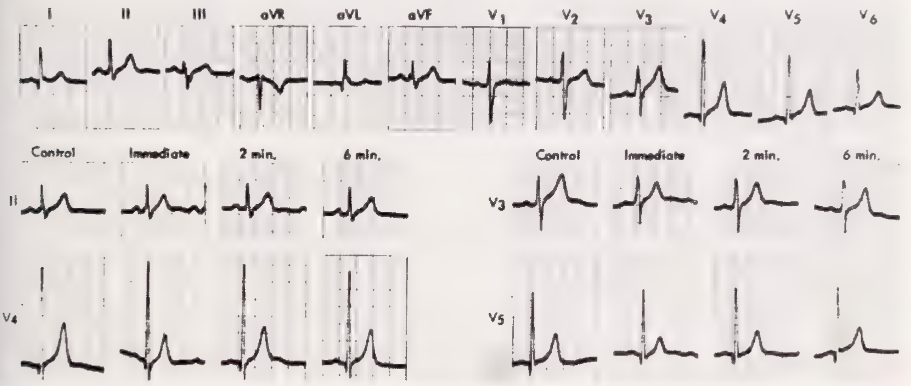


FIG. 10. F.M., male, aged 22 and athletic. He had no complaints but he had an idiopathic dilatation of the pulmonary artery with a loud systolic blow over this area. The upper row discloses a normal 12-lead resting electrocardiogram. Then the control and post-exercise tracings as shown in lead II, V3, V4 and V5 are normal. On the strength of this negative two-step test he was accepted by the army. (Dis Chest 51:347–383, 1967).

The Ischemic Depression

At first we called any type of change in the S-T segment on the exercise ECG "possibly innocuous," "possibly abnormal," or "definitely abnormal," depending entirely on the correlation with clinical findings as to whether the changes were of a functional or organic basis. Along came Paul Wood of London in 1950, who clarified the interpretation of the S-T segment depression (21). He described the "ischemic" depression in the S-T segment and now we use his definitions. He considered the horizontal or sag depression organic or "ischemic" in origin when seen on the post-exercise two-step test.

We first employed three leads in electrocardiography and then four leads. During World War II, twelve leads came into use.

Walking through Angina

Kattus (25) had advocated "walking through angina." This is permissible in a university setting with resuscitative apparatus at hand. However, as a general practice it is dangerous and we offer this illustration (Fig. 11) of a patient who learned this after a bitter personal experience.

This man walked to my office to keep an appointment. On the way he experienced chest pain but nevertheless did not stop or slow down. He continued to walk despite his pain. He wanted to "walk off the pain." By the time he reached the office, he had severe chest pressure and was in near collapse. The resting electrocardiogram was abnormal with depressions in the RS-T segments and changes in the T wave, changes characteristic of acute coronary insufficiency or subendocardial infarction. He was put to bed. It was two months before the electrocardiogram returned to normal. This, then, illustrates the danger of "walking through angina" for the ordinary patient.

Subendocardial Infarction versus Transmural Infarction

Many years ago my colleagues and I became aware that there were three types of coronary artery disease, each a separate entity. We divided arteriosclerotic coronary heart disease into three syndromes: (1) angina pectoris, (2) "subendocardial" ischemia, necrosis or infarction (acute coronary insufficiency), and (3) transmural infarction (coronary artery occlusion or thrombosis). The common basis was usually arteriosclerosis or atherosclerosis. There were three entities with regard to mechanism, physiology, precipitating causes, etiology, pathology, electrocardiography, prevention and treatment.

This demonstration that each of these three syndromes was a completely separate entity is something we worked out (26–28). Others, particularly the Germans, (29) had found there were two types of electrocardiograms in heart attacks, one indicating subendocardial injury and the other transmural infarction. One investigator reported that the pathologic findings in the two types of myocardial infarction differed; still another stated that the precipitating factors varied in the two types of heart attacks, another reported that coronary insufficiency, that is, subendocardial ischemia, necrosis or infarction, was one

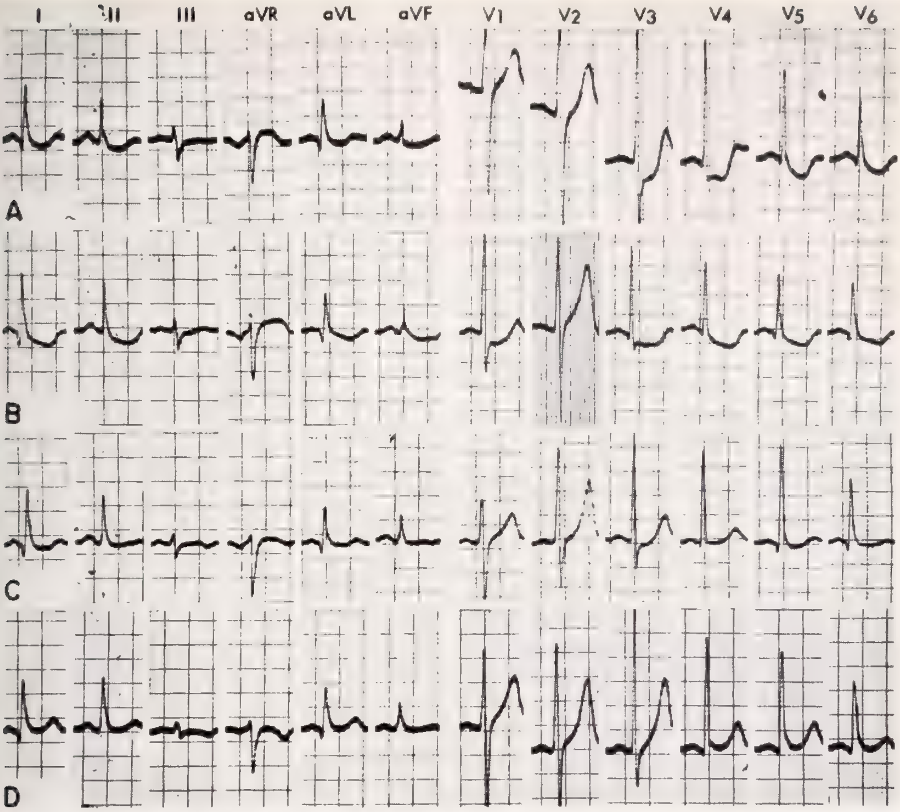


FIG. 11. A.N. a man of 39, with angina pectoris, on his way to my office experienced chest pain but kept on walking at a fast pace because he wanted to "walk off the pain." On reaching my office the chest pressure was severe and the patient was near collapse. The tracing taken at the office showed ischemic RS-T segment depressions and inverted T-waves, characteristic of acute coronary insufficiency or subendocardial infarction. He subsequently recovered and the tracing 2 months after the incident is normal. This was a case of subendocardial infarction (RS-T and T-wave changes but no Q-waves). (G.P. 31:122 (Oct.) 1965).

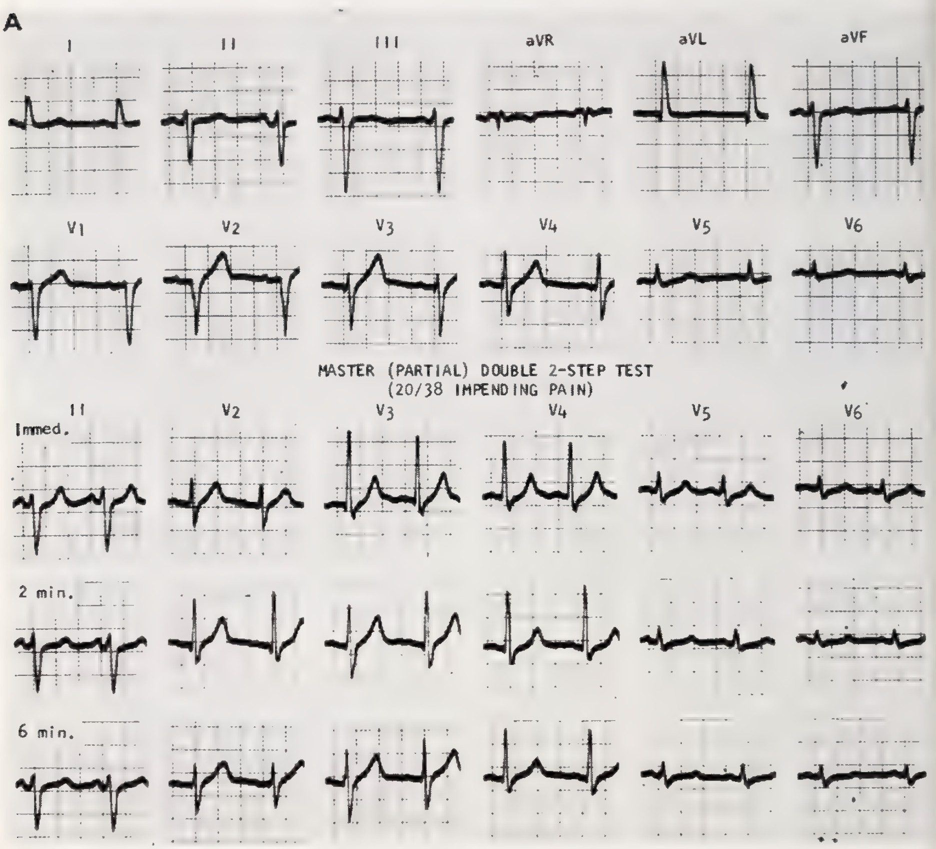
entity and that transmural infarction (coronary occlusion) was another. As we have said, the two differ in physiology, etiology or precipitating factors, pathology, clinically and laboratory-wise, in electrocardiogram and in mode of treatment (26–28).

Silent Coronary Disease

We have advocated the use of the two-step test to uncover latent, i.e., completely asymptomatic, heart disease (30). We have shown that millions of people suffer from it, as demonstrated by the resting and/or post-exercise ECG, whether or not symptoms subsequently appeared. In any case, such a patient was to be treated immediately as a potential candidate for heart disease or for heart disease already plainly evident although silent.

We were not the originators of "silent" coronary disease as such. Isolated clinicians and pathologists had mentioned it, but we actually demonstrated the vast magnitude of silent coronary artery disease. It is so ubiquitous and serious in its consequences that the physician must always be on the alert for it.

If the two-step electrocardiogram is abnormal and the patient has no complaints, he should be treated as a "potential" cardiac patient. He should be seen yearly or even every six months. If he is overweight, he should lose weight; if he has high blood pressure, he should be treated with antihypertensive agents. If the patient has hyperuricacidemia, appropriate drug therapy should be instituted. If the patient is smoking cigarettes, he must stop. If he has diabetes,



Figs. 12A & 12B. J.G., male, aged 55 with "impending angina" and an old coronary occlusion. (Figure 12A). The upper two rows show the earmarks of an old infarction, an rS in V1 and V2 but otherwise the electrocardiogram is essentially negative. The patient stopped on the 20th trip although he did not have pain but he knew that were he to continue another 2 or 3 trips, he would suffer chest pressure. The ECG after exercise was entirely negative. This we call "impending pain". It is only if the patient walks on further that ischemic depressions of the RS-T segment become apparent (Figure 12B). All this has an important clinical application. (Chest 59:125–127, 1971).

therapeutic means to control it should be taken. If the patient is sick and physically too active, strenuous exertion should be avoided. I would think twice about permitting him to jog. At the other extreme, if the man is very sedentary, he should be encouraged to do more physically. If the patient has cardiac irregularities, he must forego coffee, tea, cokes, all caffeine-containing drinks and in addition the administration of an anti-arrhythmic drug may be necessary. We teach our patients to take their own pulse, an easy measure indeed. We can thus gauge the dosage of the therapeutic drug by the presence and number of irregularities per minute.

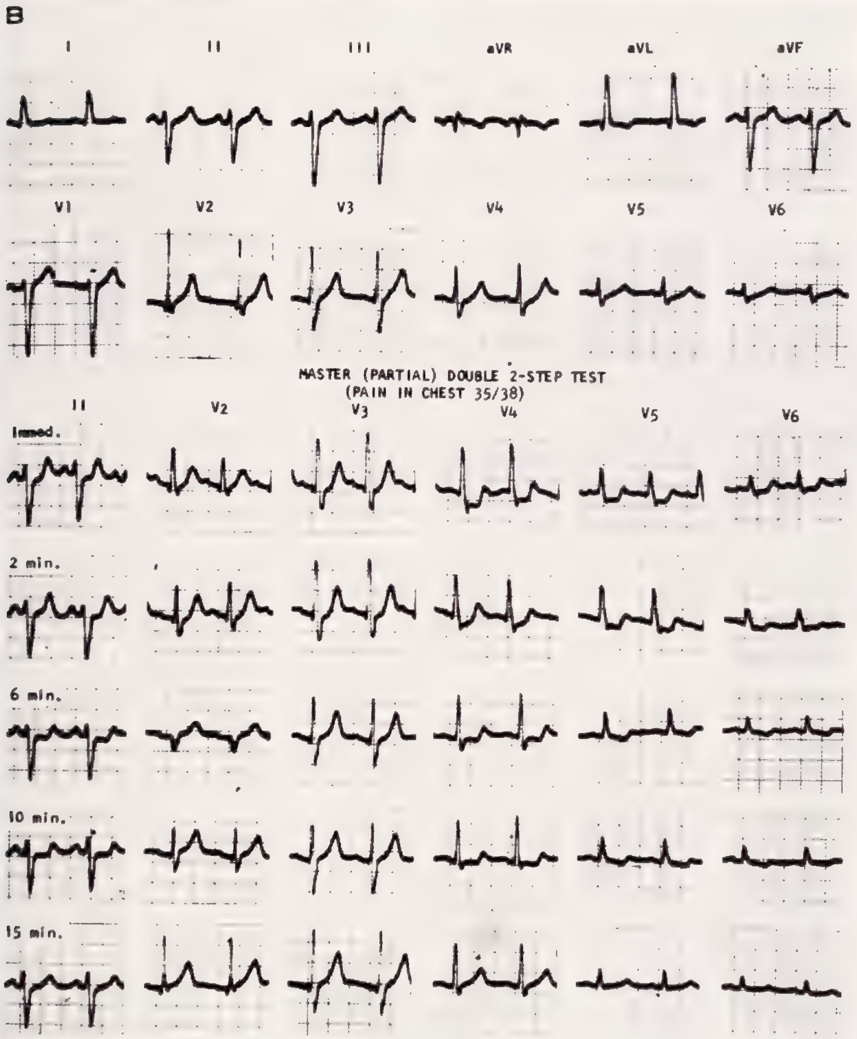

B
I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
MASTER (PARTIAL) DOUBLE 2-STEP TEST
(PAIN IN CHEST 35/38)
II
V2
V3
V4
V5
V6
Immed.
2 min.
6 min.
10 min.
15 min.

FIG. 12B.

The Two-Step versus More Strenuous Exercise Test

University research workers often advocate a more strenuous exercise test than the two-step test; they intimate that the increase in heart rate attained in the two-step exercise is not great enough. We disagree decidely with this. In order to determine "physical fitness" a more strenuous test is indicated once the man has passed the Master two-step test, but for the elucidation of coronary artery disease the two-step test is adequate and a more strenuous one may be dangerous. For the discovery or confirmation of heart disease, the increase in heart rate in the Master two-step test is completely adequate and a steady state is reached in the last 30 to 60 seconds.

Safety of the Two-Step Test

We have pointed out that one feature that makes the two-step test safe is the admonition to the patient to stop walking the moment he senses any chest discomfort. We have learned that a patient can often sense that if he made another two or more trips on the steps he would experience definite chest pain, pressure, heaviness, and other indications. If he stops at that moment, a moment we have called "impending angina" (Fig. 12A), the post-exercise electrocardiogram will be negative. (31) If the same patient were to return on the following day and, encouraged by my presence, walked two or three more trips or actually completed the test, abnormal ischemic changes in the S-T segment would invariably appear (Fig. 12B). All this has an important clinical application. We teach our patients to become introspective and to watch for the slightest suggestion of chest pain or discomfort and, if detected, to immediately stop whatever they are doing. After a short rest, they will be able to resume their activity even better than before.

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UNUSUAL PROBLEMS IN SURGERY

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JULIUS J. LEICHTLING, M.D., COEDITORS

Giant Ovarian Cyst in an Infant: Report of a Case

Cysts of the ovary are uncommon in infants and therefore are rarely considered in the differential diagnosis of abdominal masses in this age group. We recently operated upon an infant with a large abdominal mass which proved to be a giant cyst of the ovary. As is usually the case, the diagnosis was made in the operating room.

Case Report

Case Report EGH #54 48 73. A. F., a full-term female infant weighing 3760 gm (8 pounds, 4 ounces) was born in July 1970, following a normal, spontaneous delivery. No abnormalities were noted on physical examination. The infant's stay in the nursery was entirely uneventful, and she was discharged at 4 days of age. The parents first noticed some enlargement of the abdomen when the child was 6 weeks old. The abdomen slowly increased in girth and at 3½ months of age, the patient was admitted for evaluation. At this time she weighed 6500 gm. (fourteen pounds, five ounces). There was no history of vomiting, abnormal bowel movements, or fever. Physical examination revealed an 8 × 15 cm smooth, mobile, nontender mass, which occupied the right upper and mid-abdomen (Fig. 1). The mass, which transilluminated, was clearly separate from the liver, and could be felt during rectal examination when pressed downward into the pelvis. The laboratory studies showed the hemoglobin to be 12.6 grams %, the white blood cell count 9,100 cells per mm^3 with a normal differential count, and a normal urinalysis. Serum electrolytes and urinary VMA levels were within normal limits. The chest x-ray was normal. Roentgenograms of the abdomen revealed that the intestines were displaced from the right side of the abdomen by a large intraabdominal mass. This was confirmed by a barium enema which demonstrated a marked displacement of the cecum, ascending colon, and transverse colon to the left of the abdomen (Fig. 2). An IVP showed a slight shift of the right ureter towards the midline, but was otherwise normal (Fig. 3).

The preoperative diagnosis was mesenteric cyst of the right mesocolon. A laparotomy was performed on November 12, 1970, through a transverse right upper abdominal incision. A large (16 × 8 cm) smooth bluish-gray cystic structure with prominent blood vessels occupied the right side of the peritoneal cavity and extended beyond the midline. The fimbriated end of the right fallopian tube was intimately attached to the cyst, but no definite ovarian tissue could be identified on its surface (Fig. 4). The left ovary was normal. The intact cyst and adherent fallopian tube were removed. The cyst weighed in excess of 600 gm and contained serous fluid. A small nodule found on the right lobe of the liver was removed for examination.

Microscopic examination showed the cyst to have a fibrovascular wall with areas of ovarian parenchyma, lined by flattened cuboidal epithelium. Microscopic follicles were present within the ovarian stroma. Several microscopic paraovarian cysts were present within the mesosalpinx. The diagnosis was simple cyst of the ovary. The liver lesion proved to be a hamartoma.

The child was discharged on the seventh postoperative day after an uneventful recovery.

Discussion

The shape and location of abdominal masses in the neonate will often be demonstrated by a plain film of the abdomen. The large amount of intestinal gas which is usually present in

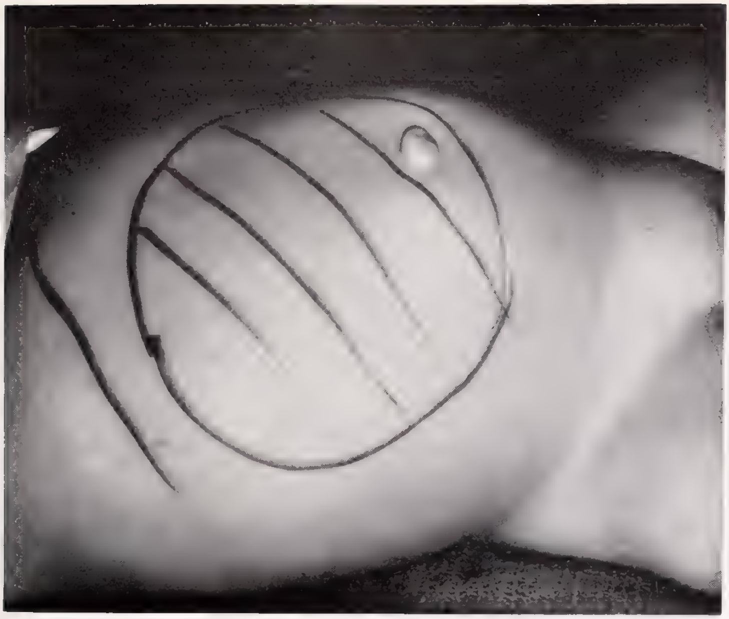

FIG. 1. Preoperative photograph—A large mass occupies the right side of the abdominal cavity.

this age group may be displaced by the mass. Further information may be obtained by the use of an upper gastrointestinal series and barium enema. Intravenous pyelography, however, is the most important diagnostic test, since masses of renal origin account for 45–50 percent for all abdominal masses. These include hydronephrosis, Wilm's tumor, and cystic renal diseases. The IVP is also important in delineating other retroperitoneal lesions such as neuroblastoma, teratoma, adrenal and pancreatic cysts. Since neuroblastoma causes an elevation of urinary VMA levels, this study should be performed when the diagnosis is suspected. A venocavagram can be done in conjunction with intravenous pyelography and may show extrinsic compression or invasion by the lesion (2). A roentgenographic bone survey and bone marrow aspiration should be performed in all cases of possible malignancy. Angiography as well as hepatic, renal, and adrenal radioisotope scanning may be useful in selected cases.

Intraperitoneal masses are usually benign and include cysts and tumors arising from the liver, spleen, gastrointestinal tract, ovary, urachus, mesentery, and omentum. These lesions will usually not affect the IVP configuration, but may be delineated by contrast studies of the gastrointestinal tract.

Ovarian cysts presenting during infancy are most often asymptomatic. They are usually benign and are rarely functional. Vomiting due to intestinal obstruction occurs, but is uncommon. Respiratory distress may be present if the tumor is large. Fever is uncommon. Torsion of the pedicle with compromise of the vascular supply is usually

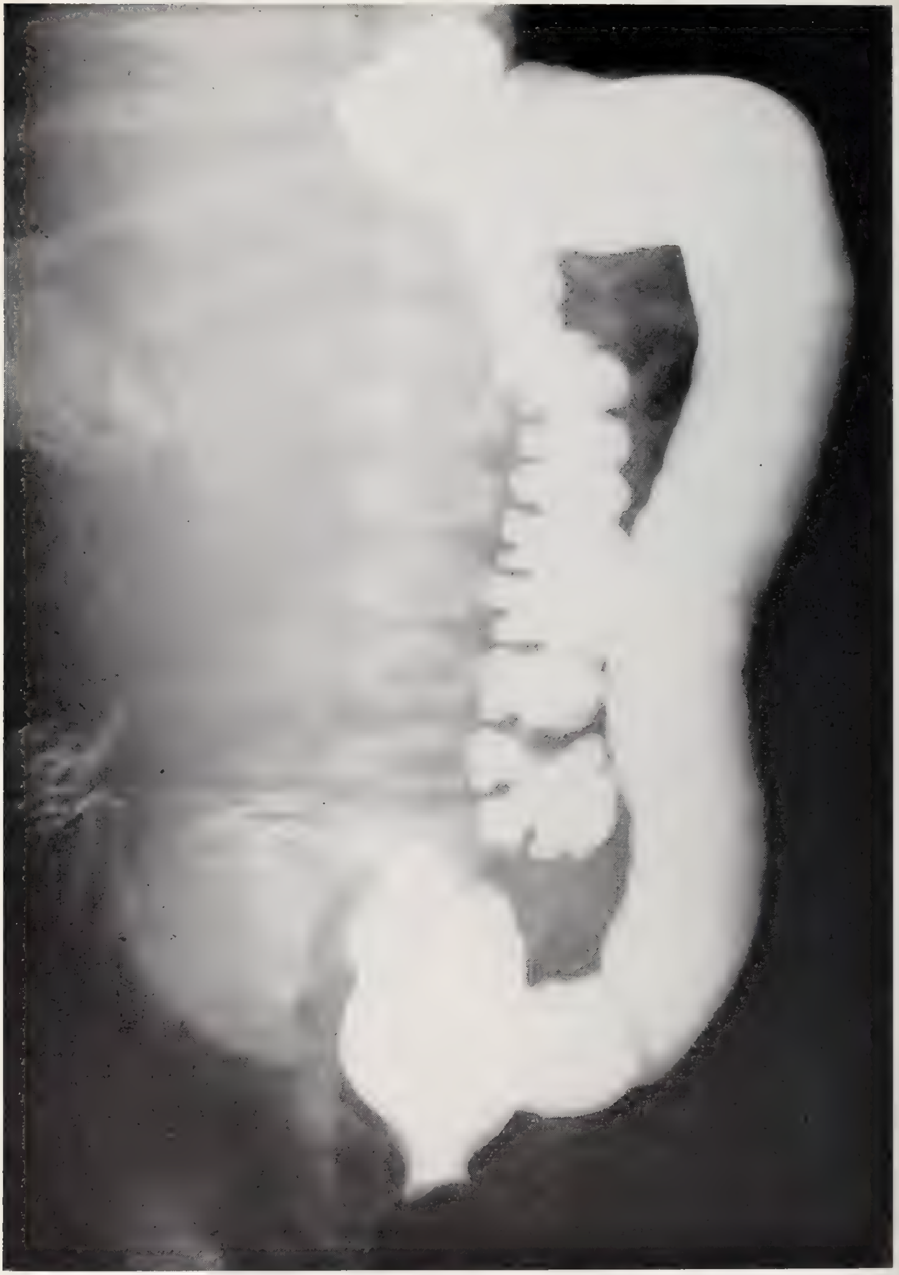

Fig. 2. Barium Enema—There is a marked displacement of the right and transverse colon to the left side of the abdomen.

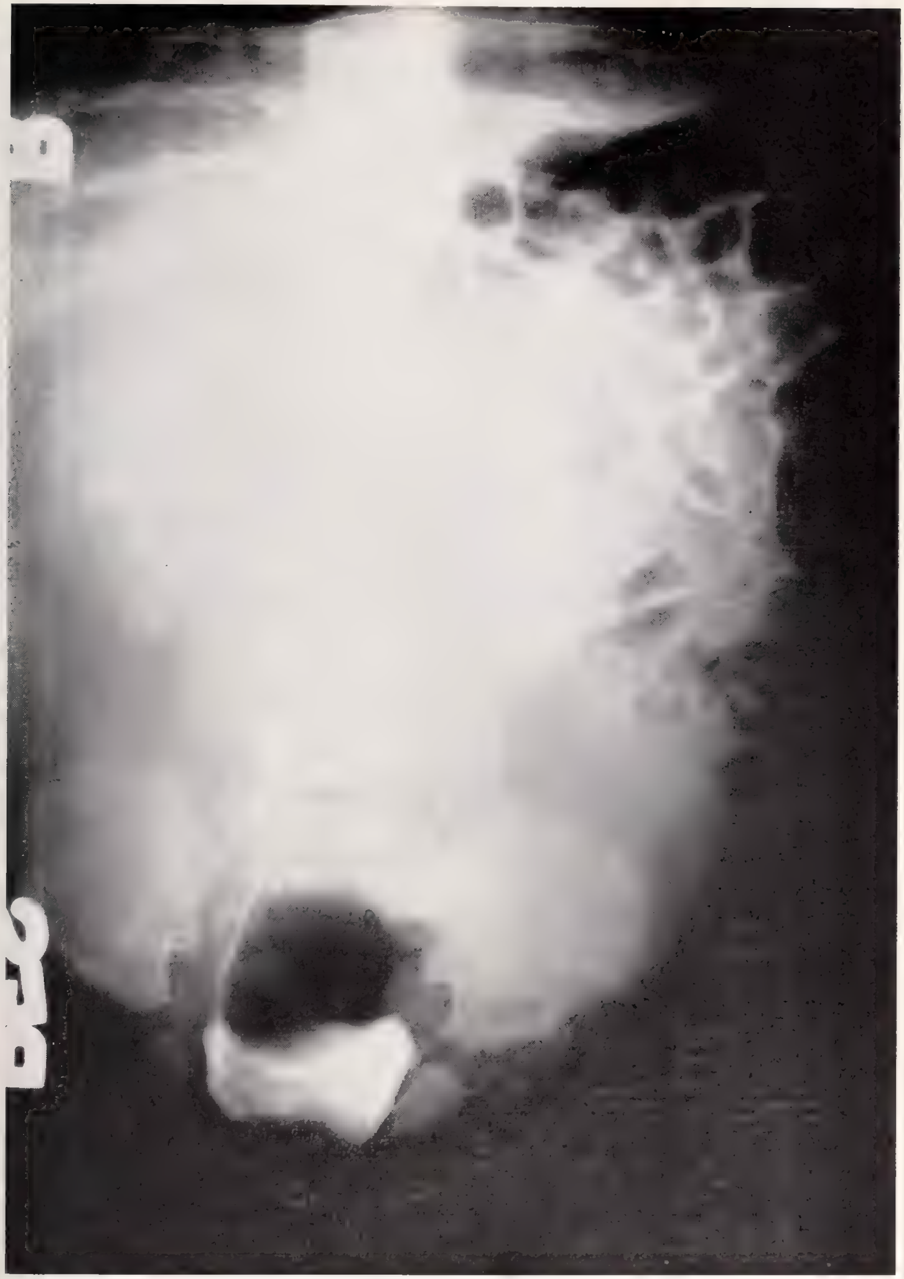

FIG. 3. Intravenous pyelogram—There is slight compression and medial displacement of the right ureter. Note hazy appearance of the right half of the abdomen and displacement of the small bowel to the left.

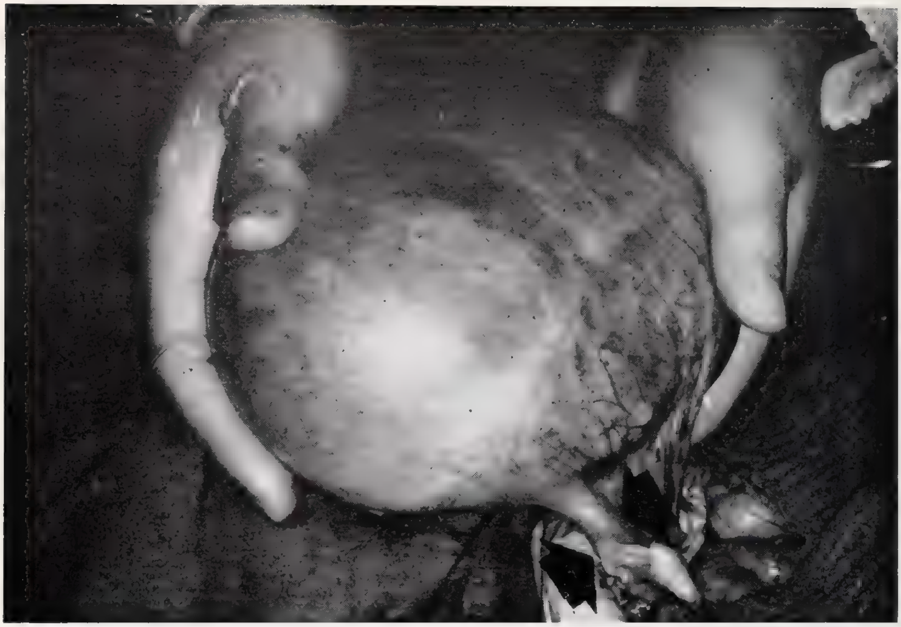

FIG. 4. Operative photograph—A large ovarian cyst containing more than 600cc. of fluid was found. Note fallopian tube (arrow).

seen in older children, but has been reported in infants (1). Peritonitis or intestinal obstruction may ensue. Rupture of the cyst may produce hemoperitoneum or ascites (1). Small ovarian tumors in infants are usually found within the pelvis. As the tumor enlarges it is displaced out of the pelvis and into the peritoneal cavity.

In a series of ovarian tumors in 75 infants and children from birth to 15 years of age, 84 percent of tumors were benign (4). Forty-six percent of benign tumors were cystic teratomas and 32 percent were simple cysts. In infants almost all ovarian tumors are benign follicular or simple serous cysts (1). In older children plain roentgen films of the abdomen are important, since calcification is frequently present in cystic teratomas (dermoids) (5). Several authors report a predominance of right-sided ovarian lesions in clinical cases. This may be due to the more frequent examination of the right ovary during surgical exploration for abdominal pain. However, Brune notes that in autopsy series, right ovarian lesions also predominate (3). Single or multiple follicle cysts of microscopic size, are a routine finding in the ovaries of the newborn, and are not considered pathologic (3). Large cysts are probably caused by maternal hormonal stimulation in utero (1).

Treatment consists of careful excision of the cyst with preservation of the ovary if possible. However, the ovary may be so attenuated over the surface of the cyst that oophorectomy must be performed. Partial or total removal of the fallopian tube may be necessary. An incidental appendectomy may be performed.

Summary

The case of a three month old infant with a giant benign ovarian cyst is

presented. Diagnostic methods for differentiation of neonatal abdominal masses are described. Diagnosis, pathology, and treatment of neonatal ovarian tumors are discussed.

A. ROBERT BECK
AND
HARRY APPLEBAUM

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RADIOLOGIC NOTES

CLAUDE BLOCH, M.D. AND HARVEY M. PECK, M.D., COEDITORS

Case No. 359

A 39-year-old woman was seen by her physician for vague abdominal complaints, and then again five years later at 44 years of age for similar vague upper abdominal symptoms. On both occasions extensive laboratory and radiographic examinations were performed. No significant disease or pathologic process was discovered at any time and no medication was prescribed. The complaints were felt most likely to be of functional origin.

History in this patient reveals no evidence of significant low back or sacroiliac pain at any time. There was no history of injury or heavy work. The patient was para II, the last child being born at the mother's age of 29.

An incidental finding at the time of the first work-up was the presence of unilateral osteitis condensans ileii on the left side (Figs. 1a and 1b). A triangular zone of dense bone at the infero-medial corner of the left iliac bone was noted extending up to the sacroiliac joint. The joint itself was not involved,

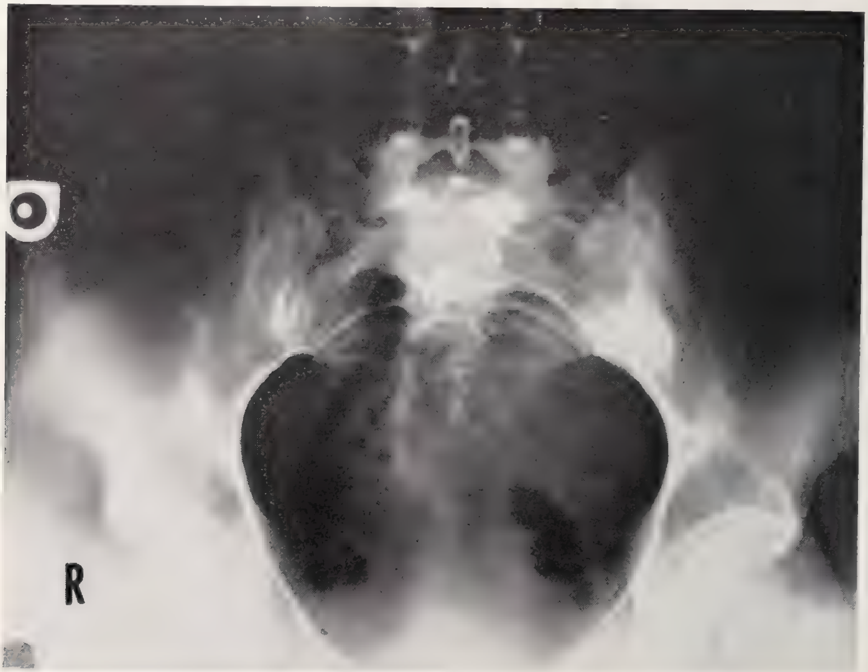

FIG. 1 a. Frontal view of the pelvis (patient age 39 years) shows unilateral osteitis condensans ileii on the left. A triangular zone of increased density is seen precisely at the inferomedial corner of the left iliac bone stopping abruptly at the sacroiliac joint. The right side is normal.

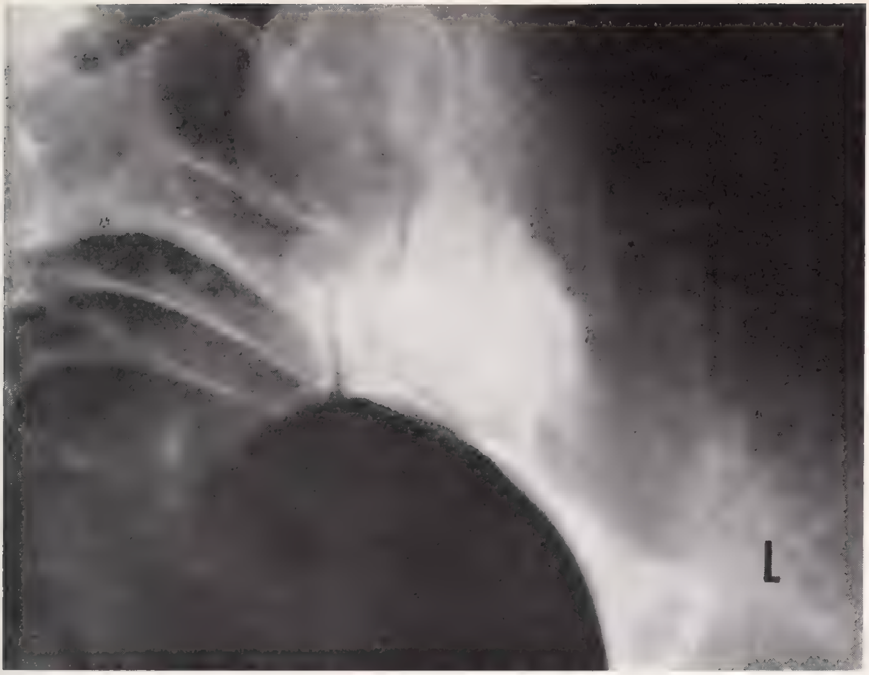

FIG. 1 b. Close-up view shows the amorphous nature of the process, its sharp demarcation, and the intact sacroiliac joint.

remained normally opened, and had smooth contours. When the patient was evaluated a second time five years later, a marked change was noted (Figs. 2a and 2b). Although one could still vaguely make out the original area of involvement, virtually all of the increased density of the bone had disappeared and a normal trabecular pattern had been restored.

Discussion

Osteitis condensans ileii is a benign self-limited condition of the iliac bone. The process is characterized by a triangular zone of amorphous density located just at the infero-medial corner of the iliac bone adjacent to the sacroiliac joint. Virtually all patients are female and the most important common denominator appears to be parturition; trauma and unusual weight-bearing have also been implicated. The condition is not related to any known systemic disease, and specifically there is no relationship to the sacro-ileitis of ankylosing spondylitis. Most patients demonstrating the condition have or have had symptoms such as low back pain or sacroiliac discomfort which could have been related to the process, but the patient is often asymptomatic when the roentgen findings are first discovered. In about one quarter of patients the process is unilateral as in the case presented, and when bilateral, is often asymmetric in extent. The surface of the sacroiliac joint itself is unaffected. Although the sacrum is

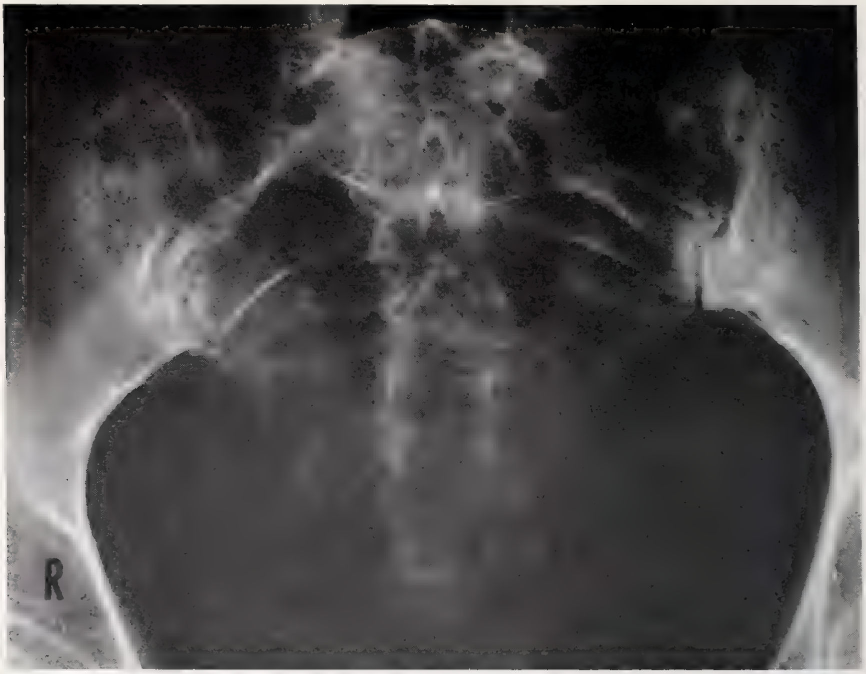

FIG. 2 a. Frontal view of the pelvis (patient age 44 years) shows virtually complete disappearance of the sclerotic osteitis on the left side with only a faint difference in density between the two sides.

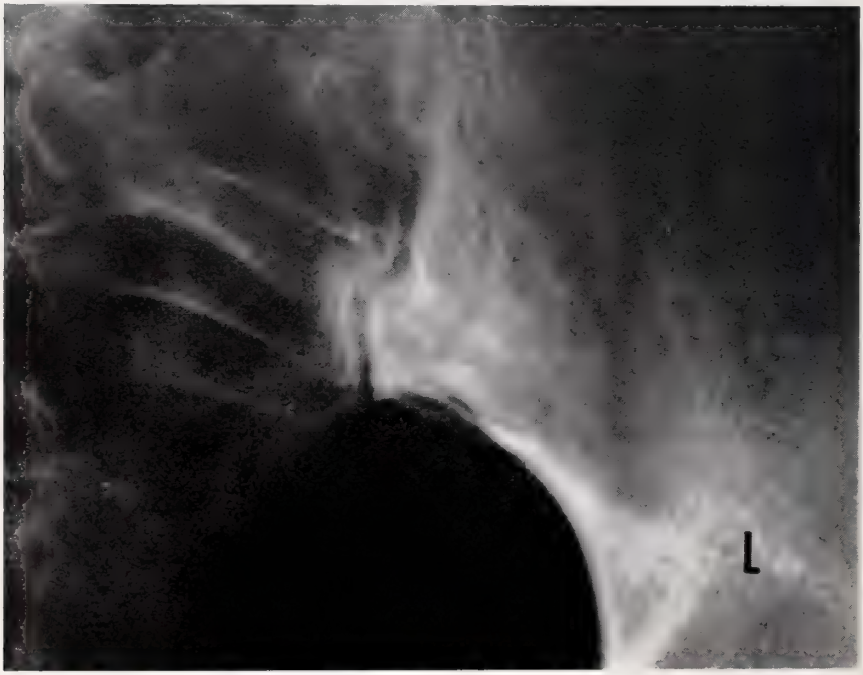

FIG. 2 b. Close-up view shows a restored trabecular pattern and very slight residual increased density. The sacroiliac joint remains intact.

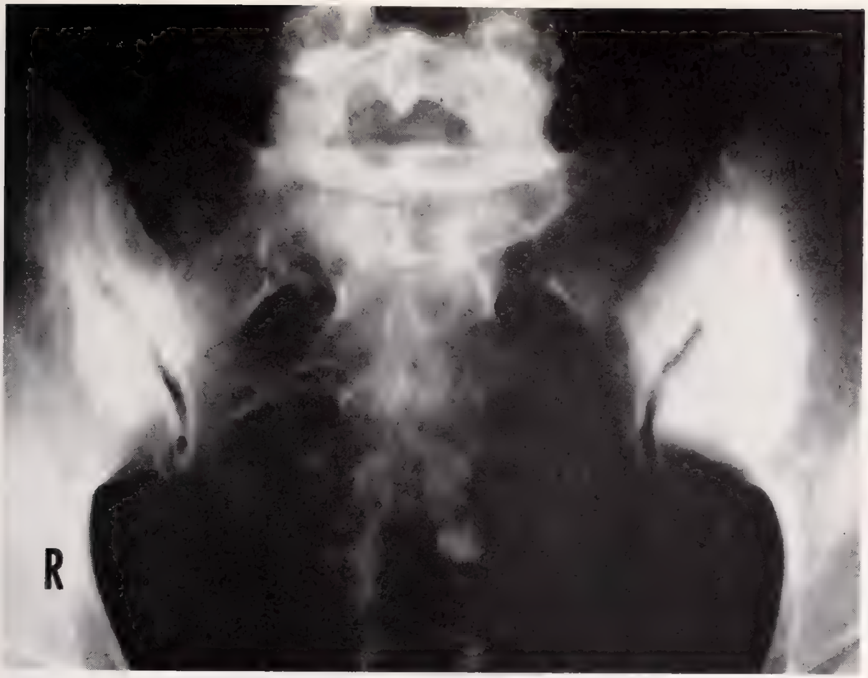

FIG. 3. Frontal view of the pelvis from another case (patient age 40 years, a grand multiparous female) shows some unusual features of the condition. The process is asymmetric and more extensive than usually seen, does not extend to the extreme infero-medial margin of the iliac bone, and involves the sacrum to some extent on each side. (This latter point was proved by tilt-up and oblique views of the sacrum and sacroiliac joints.) This patient had significant low back and sacroiliac joint symptoms.

usually spared, in a small percentage of cases the adjacent sacrum may be involved to a lesser extent. Biopsy reports have revealed dense bone without structure, presumably due to aseptic necrosis. Abnormal blood supply to this area may be postulated but the vascular factors have not been elucidated.

It has been noted that the process usually occurs in the third through fifth decade and is unusual thereafter. This has led to the presumption that the process can heal. The case presented documents and establishes this presumption. Within an interval of five years, a typical zone of amorphous dense bone was reconstituted into normal appearing bone having a normal trabecular pattern, with disappearance of virtually all of the initial increased bone density (Figs. 1 and 2).

An illustration from another case is presented in order to demonstrate some of the more atypical features (Fig. 3). In this case, the zone of density did not extend inferiorly all the way to the corner of the iliac bone but was more centrally placed. The process was asymmetric and more extensive than usually seen. There was moderate involvement of the sacrum on each side which was confirmed by tilt-up and oblique views of the sacrum and sacroiliac joints (not shown).

Case Report: OSTEITIS CONDENSANS ILEII WITH HEALING

Acknowledgments

This case is presented through the courtesy of Dr. Peter Shershin, Good Samaritan Hospital, Suffern, N.Y.

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Case No. 360

A 45-year-old male was referred for excretory urography prior to repair of a left flank incisional hernia. Ten years previously the patient underwent left ureterolithotomy through a flank incision. The report of an excretory urogram performed at that time states that "the kidneys were normal in size, shape, and position"; these films are no longer available for review. An incisional hernia developed in the immediate postoperative period. It eventually reached a size easily admitting four or five fingers. The patient refused reparative surgery. Over the course of the intervening ten years the hernia was responsible for local discomfort and limitation of general physical activity. There were no abnormal urinary symptoms.

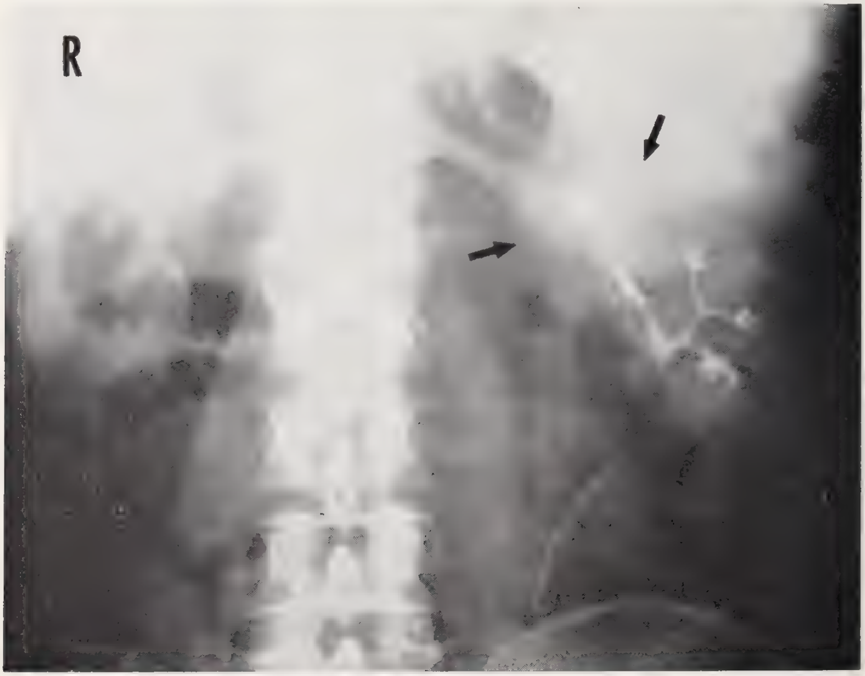

FIG. 1. Frontal view of the abdomen during excretory urography shows good function bilaterally. The right kidney is normally oriented. The left kidney is not seen in its normal paravertebral location but instead is located infero-lateral to its usual position. In addition, the kidney has rotated on its antero-posterior axis with the lower pole reaching the flank. There has been some rotation on its vertical axis as well.

Excretory urography was performed (Fig. 1). Both kidneys functioned well. The right kidney was normally oriented. The left kidney was located infero-lateral to its usual paravertebral position. It was rotated on its antero-posterior axis with the lower pole reaching the left flank. There was some rotation on its vertical axis as well. The size of the kidney and the width of the renal parenchyma were normal and there was no obstruction. No calculi were present.

At surgery, the abnormal position of the left kidney was confirmed. Nephropexy and repair of the flank incisional hernia were performed in routine fashion.

Discussion

In analyzing abdominal films with respect to the presence of mass, whether intraperitoneal or retroperitoneal in location, the position of the renal outlines is critical to the analysis. Accordingly, radiologists are trained to look for the kidney shadows and to note their relationships to the fixed musculo-skeletal structures (vertebral bodies, lower ribs, iliac crest, and psoas muscles) their relationships to the intraperitoneal viscera, and their relationships to each other. The analysis is extended to include the position of the ureters as well. Displacement of kidneys or ureters is usually thought of in terms of a mass effect, i.e., a pressure effect from a space-occupying process. Another cause for displacement which may be overlooked is that due to the presence of hernia. In this case, displacement is due to a deficiency in the wall of the body cavity acted on by the normal intraabdominal forces. Also, there is considerable anatomic variation in the location of the kidneys. Caution is advised in deducing the presence of a mass based solely on the position of the renal outline.

Case Report: DISPLACED KIDNEY DUE TO FLANK INCISIONAL HERNIA

Case No. 361*

A 52-year-old male with moderately severe Parkinson's disease had a history of difficulty in voiding and incontinence. He also had a long history of enlargement of the left hemi-scrotum, occasionally painful. He was admitted to the hospital for urological evaluation and surgical excision of what was thought to be a left hydrocele.

Physical examination revealed marked enlargement of the left hemi-scrotum which was nontender, cystic in consistency, and which transilluminated. Excretory urogram and retrograde cystogram were performed (Figs. 1–3). The left aspect of the bladder showed a peculiar triangular tented configuration. The superior contour of the bladder had a humped or lobulated appearance. The bladder and trigone were shifted toward the left. When the bladder was filled in retrograde fashion during a cystogram, a large herniated portion of the bladder located in the scrotum was filled with opaque material. These findings were not demonstrated on the intravenous study at which time the scrotal region was not included on the film.

Cystoscopy revealed a small opening on the left lateral wall of the bladder

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* From the Department of Urology, Good Samaritan Hospital, Suffern, New York.

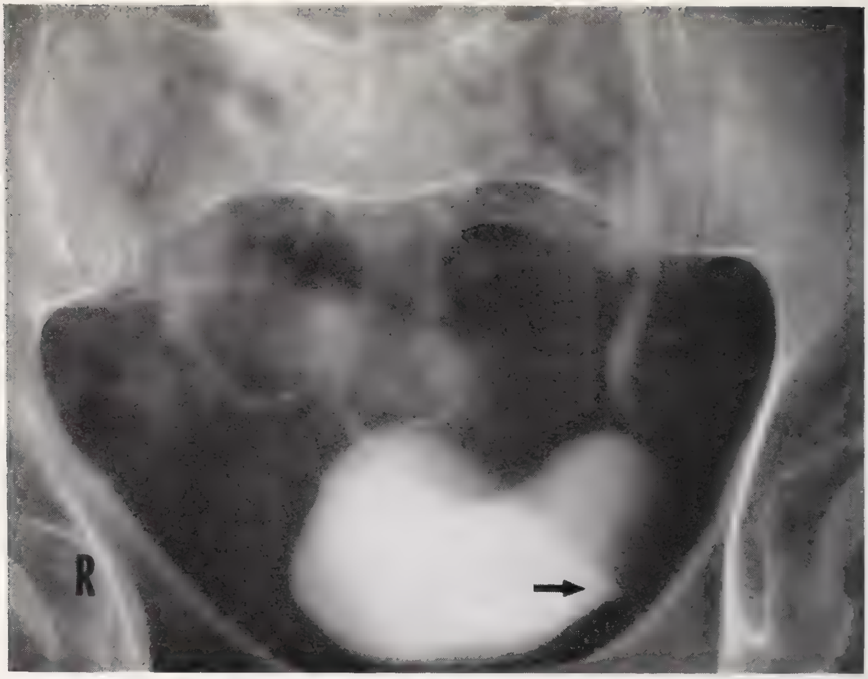

Fig. 1. Frontal view of the bladder during excretory urogram shows a peculiar triangular pointed contour on the left aspect of the bladder (arrow). The superior contour shows a peculiar humped configuration. The bladder is displaced somewhat to the left.

above the ureteral orifice which represented the entrance to the hernia. At surgery, the bladder hernia was traced through the inguinal ring into the scrotum; a conventional inguinal hernia was also noted. The bladder hernia was excised and the inguinal hernia repaired.

Discussion

Herniation of the bladder is not infrequent and occurs in a small percentage of cases of inguinal and femoral hernias. The inguinal variety is much more common and is usually found in males, while the femoral variety predominates in females. True scrotal herniation of the bladder is quite rare. After dissecting out the hernial sac and establishing its relationship to the inguinal ring and the peritoneum, the herniated bladder may be classified as extra-peritoneal, intraperitoneal, or para-peritoneal. The latter is the most common variety, as was the case presented, in which the herniated portion of the bladder lies adjacent to one wall of an inguinal hernia sac. The roentgen finding of a tented configuration to the bladder contour should alert the radiologist to the possibility of bladder herniation (Figs. 1 and 4). The deformity of the bladder and the displacement of bladder and trigone will depend on the extent of the hernia.

The differential diagnosis between hydrocele and herniation of the bladder is difficult if the latter condition is not suspected. Excretory urography with cysto-

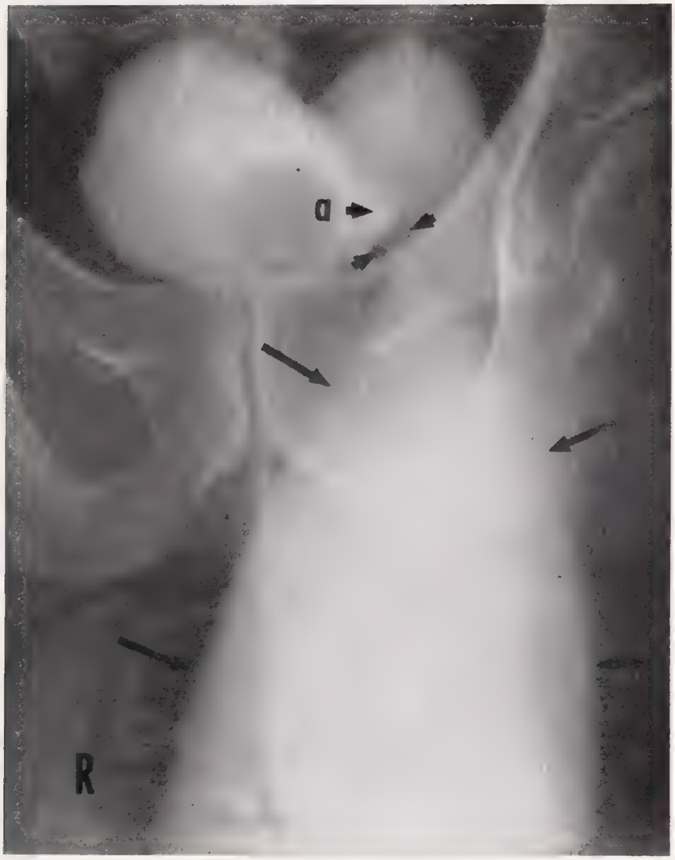

Fig. 2. Frontal view of the bladder and scrotal region from a retrograde cystogram again shows the triangular tented configuration to the left aspect of the bladder (arrowhead a). Opaque material fills a large herniated portion of the bladder (lower arrows). The narrow neck of the herniated bladder is seen (between arrowheads). A Foley balloon catheter is in situ.

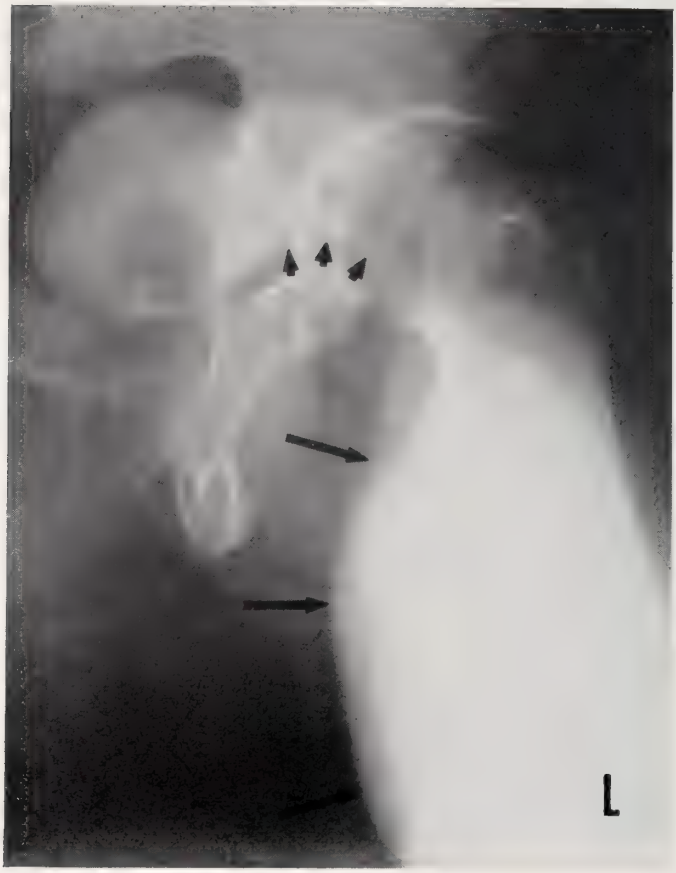

Fig. 3. Left posterior oblique view of the bladder and scrotal area from retrograde cystogram shows the curving course to the neck of the hernia as it crosses the superior pubic ramus (arrowheads). The herniated bladder in the scrotum is well filled with opaque material (arrows).

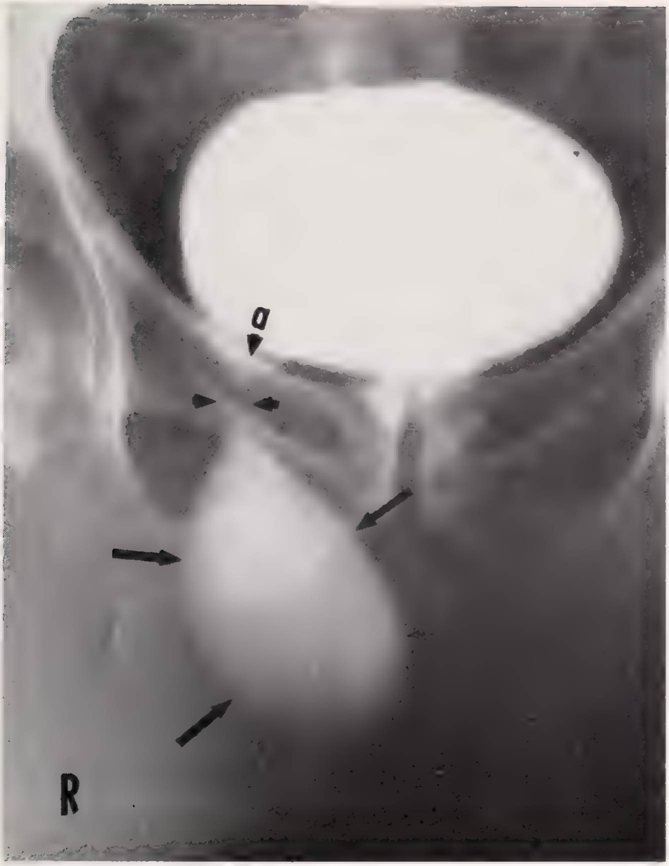

Fig. 4. Frontal view of the bladder and scrotal region in another case of herniated bladder in an elderly male patient. Note the triangular pointed bladder contour adjacent to the hernia (arrowhead a), the narrow constricted neck of the hernia as it crosses over the superior pubic ramus (between arrowheads), and the herniated bladder itself in scrotum, well filled with opaque material (lower arrows).

gram should be considered pre-operatively in all patients with hernia or hydrocele particularly in the older age group.

Case Report: URINARY BLADDER HERNIATION INTO THE SCROTUM

MARVIN BUTTERMAN, M.D.

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Case No. 362*

A 49-year-old man fell while getting out of his car and sustained an injury to his right arm. Interpretation of the description of the injury suggests that a condition of forced supination occurred. Following injury, the patient was unable to pronate or supinate the forearm without discomfort. Physical examination revealed the forearm in approximately 40° supination. There was a prominent bulge over the volar surface of the ulnar head and a prominent hollow dorsally. Neurologic examination showed no deficit. The patient was able to extend and flex the wrist to about 30° in each direction. He could supinate the forearm about 40° but could not perform pronation because of pain.

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Radiographs of the wrist revealed a dislocation of the distal radio-ulnar joint, with the ulnar head displaced volarward (Fig. 1 a, b, and c). Subsequently, the patient was anesthetized and satisfactory reduction was easily accomplished with digital pressure. A long-arm cast was applied with the wrist in neutral position and with the forearm in neutral rotation (Fig. 2a and b).

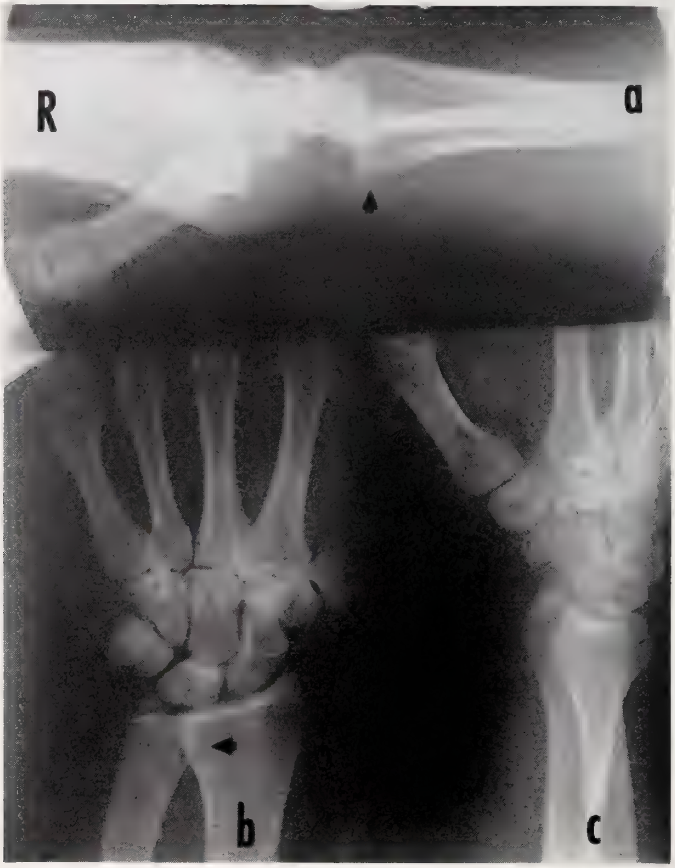

FIG. 1 a. Lateral view of the wrist shows the distal end of the ulna to be located volarward in relation to the radio-carpal joint (arrow). Since this lateral view is well positioned, a volar dislocation of the ulna can be diagnosed. b. Ventro-dorsal view of the wrist shows overlapping of the distal radius and ulna (arrow). Since this anteroposterior view is well positioned, radio-ulnar dislocation can be diagnosed. The action of the pronator quadratus muscle causes this overlap only when the ulna is dislocated in a volar direction. c. Slight pronation oblique view of the wrist obscures the volar ulnar dislocation.

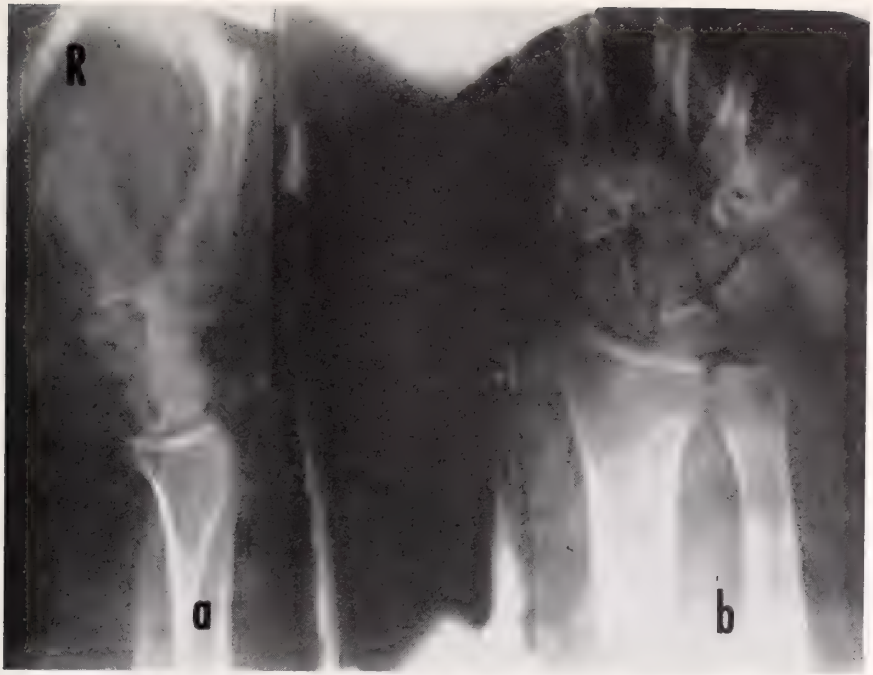

FIG. 2. Well-positioned lateral (a) and dorso-ventral (b) views of the wrist through plaster show the relocated radio-ulnar joint.

Discussion

Traumatic fracture-dislocation of the distal radio-ulnar joint is a common injury; dislocation without fracture, however, is rare. Most authors feel that the rotary motions at the wrist are performed by the radius with relation to the carpal bones since the ulna at the wrist is fixed. If the radial-carpal complex is forced into hyperpronation, the distal ulna may be dislocated dorsally. Conversely, if the radial-carpal complex is hypersupinated as in the case presented, the distal ulna may be dislocated volarward. From the clinical viewpoint, early diagnosis is important so that a closed reduction may be performed easily with the expectation of an excellent result. Failure to recognize the injury may result in the necessity of performing an open-reduction at a later date. From the roentgen viewpoint, carefully positioned films are essential to arrive at the correct diagnosis. A true lateral view clearly shows the volar dislocation in the case presented (Fig. 1a), but this is obscured in a slight oblique projection (Fig. 1c). The clue to the dislocation in the frontal projection is the overlapping of the distal radius and ulna (Fig. 1b). This results from the action of the pronator quadratus muscle. In the hypersupination injury with volar dislocation, the action of the muscle pulls the ulnar head radialward thus overlapping the two bones in the frontal projection. In the hyperpronation injury with dorsal dislocation, its action separates the two bones resulting in a space between them in the frontal projection.

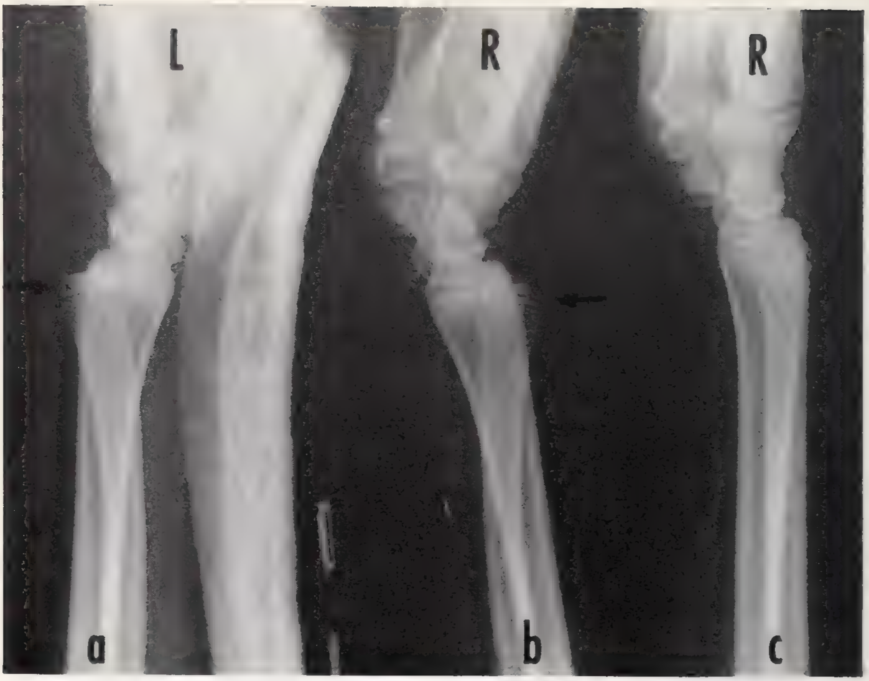

FIG. 3. A case of suspected dorsal dislocation of the distal ulnar. a. and b. Simultaneous lateral views of both wrists positioned midway between pronation and supination in the usual fashion. A volar plaster splint on the left side was applied as a precautionary measure following injury. Note the dorsal position of the ulnar heads, bilaterally symmetrical. Dorsal dislocation was suspected until comparative view was obtained. Patient had symmetrically prominent ulnar heads, an anatomic variation; there was no tenderness or abnormal function. c. Repeat lateral view of the right wrist made with the forearm in supination (elbow at 90°, shoulder lowered to the horizontal level of the wrist), shows a more normal appearing relationship. The ulnar head does not project dorsally to any great degree (Compare this with b). Note that the shafts of the radius and ulna are parallel.

In further regard to accurate positioning, Figure 3 is from another case which illustrates the problem in arriving at the correct diagnosis of dorsal dislocation of the ulnar head. This patient has bilaterally symmetrical dorsally prominent ulnar heads with no disfunction or limitation of motion. Initial lateral view following injury suggested dorsal dislocation (Fig. 3a). Simultaneous exposure of lateral views of both wrists established the symmetrical condition (Fig. 3a and b). Note that the standard lateral projection midway between pronation and supination was employed. A true lateral projection made with the forearm in full supination (elbow held at 90° and shoulder lowered to the horizontal plane of the wrist) is not at all impressive (Fig. 3c). Note the parallel course of the shafts of the radius and ulna when positioned in this fashion.

Case Report: ANTERIOR DISLOCATION OF THE ULNA AT THE INFERIOR RADIO-ULNAR JOINT

MARTIN POPOWITZ, M.D.

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Case No. 363*

A 40-year-old woman, para 3003, was admitted to The Mount Sinai Hospital with a history of long-standing menometrorrhagia unresponsive to hormonal therapy. Prior to admission to the hospital, hysterosalpingogram was performed in a radiologic office.

Excretory urogram performed during the preoperative evaluation showed no intrinsic abnormality to the urinary tracts. Opacified lymph nodes in the left inguinal region were seen. In addition, there was a small collection of tiny opaque densities on the right side of the pelvis, which had not been present on a plain film of the abdomen made previously (Figs. 1 and 2). Both these collections of opaque material were felt to represent residual oily contrast medium employed in the recent hysterosalpingogram.

Patient underwent a total abdominal hysterectomy for a fibroid uterus and made an uneventful recovery. The specimen showed a fibroid uterus with myomata blocking both cornua.

Discussion

The presence in the inguinal lymph nodes of the oily contrast medium employed in previous hysterosalpingography documents a rare complication of this procedure which occurs in about 1 percent of all cases, viz., intravasation of opaque material into veins or lymphatics. Intravasation is more frequent in patients with intrauterine filling defects such as myomata. Obstruction of a cornu also tends to elevate the pressure in the uterine cavity during hysterosalpingography. In the case presented, there were myomata in both cornua which probably was a predisposing factor. Lymphatic intravasation is only very rarely demonstrated by opacification of lymph nodes, and then is almost always associated with tuberculous involvement of the endometrium; there was no evidence of tuberculosis in this case.

The inguinal lymph nodes usually drain internally to the iliac and then aortic lymph nodes. The reason for retrograde filling of the inguinal nodes is not clear in this case.

Case Report: LYMPHATIC INTRAVASATION AND OPACIFICATION OF INGUINAL LYMPH NODES FOLLOWING HYSTEROSALPINGOGRAM

ALFRED ROSENBAUM, M.D.

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* From the Department of Radiology, The Mount Sinai Hospital, New York, N.Y. 10029.

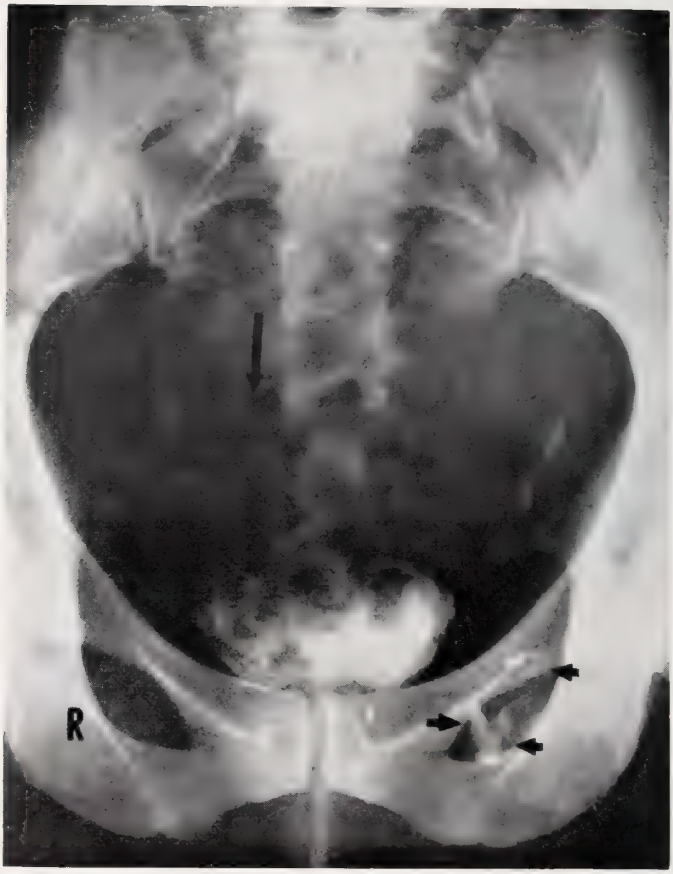

Fig. 1. Post-voiding film from intravenous pyelogram shows residual contrast material in the partially collapsed bladder and small collections of contrast material in segments of both pelvic ureters. A collection of opaque material is seen overlying the obturator foramen on the left side (lower arrows). This represents opaque material from previous hysterosalpingogram, now located in left inguinal lymph nodes. On the right side of the pelvis, there is a small collection of very tiny densities which represent residual intraperitoneal opaque material from previous hysterosalpingography (vertical arrow, virtually lost in reproduction).

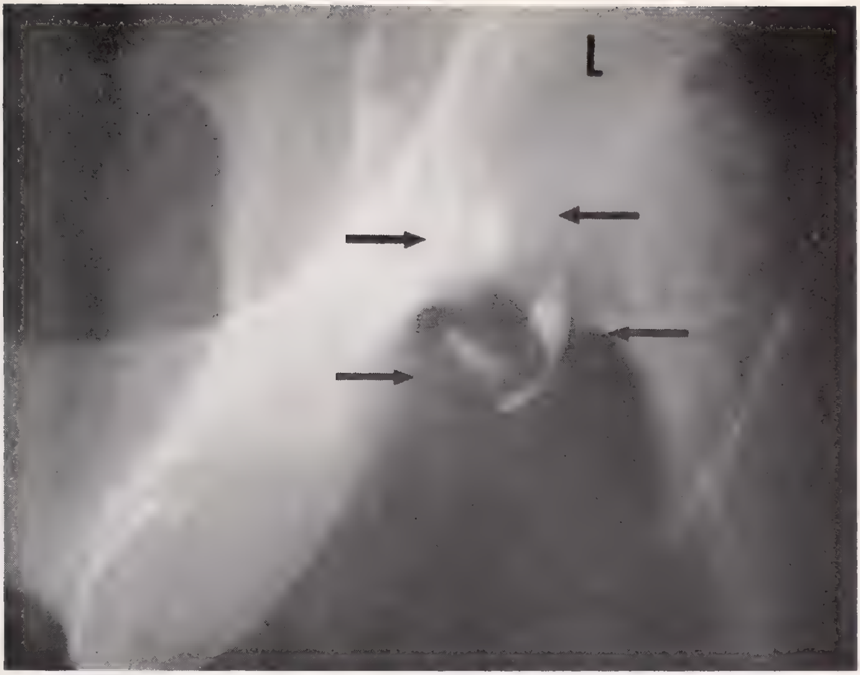

FIG. 2. Left posterior oblique view confirms the anterior location of the opaque material in the left inquinal lymph nodes.

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WILLIAM ANTOPOL, M.D.
1903–1972

In Memoriam

WILLIAM ANTOPOL, M.D.

1903–1972

Dr. Antopol was born 69 years ago, in New York City. He graduated from the College of the City of New York in 1923 and received his medical degree from the Long Island College of Medicine in 1927. Following an internship at Brookdale Hospital in Brooklyn, he was awarded the George Blumenthal (1928) and the Theodore Escherich (1929) Fellowships in Pathology at The Mount Sinai Hospital. He continued his training and research at the same institution as Assistant in Pathology from 1930–1935. In 1930, at age 27, he published the first of his 216 papers. His eagerness for broader knowledge and his need to widen his horizons took him to Leipzig and Vienna in 1931. At the University of Vienna he was privileged to study with Professors Pick, Silverstein, and Rothberger. He returned to Mount Sinai where he was inspired and motivated for scientific investigations in a milieu of constant intellectual ferment. He worked in the scholarly atmosphere created by men like Klemperer, Otani, and Shwartzman.

In 1932, he was awarded his first grant by the American Medical Association for studies on acetylcholine and cholinesterase. This was the beginning of an outstanding career in medical research which has been supported by governmental agencies, and by private organizations and individuals. His research covered a broad spectrum of pathophysiologic phenomena ranging from lycopodium granuloma and the effects of sulfonamides, vitamins, and cortisone, to the mechanisms of the Shwartzman reaction, dysbaric disorders, and drug addiction. Realizing the limitations of pathology in the study of such diverse conditions, he collaborated with biochemists, pharmacologists, and other scientists, while he broadened his education in overlapping disciplines. Many of his scientific investigations gained for him an international reputation.

Meanwhile, an established pathologist, he became Director of Laboratories and Research at Beth Israel Hospital in Newark, N.J. (1935–49). In 1949 he was appointed Pathologist-In-Chief, Director of Laboratories and Research at Beth Israel Hospital in New York, an institution to which he devoted the latter part of his professional life. In 1955 his life was saddened by the early death of his beloved wife, Bella, who gave him their two sons, Dr. Michael Antopol and Stephen Antopol, a medical student at New York University.

An old proverb known to woodsmen says: "A tree is best measured when it is down." The tree is down but it is still hard to assess its dimensions. I have known William Antopol since 1956. In the sixteen years of our association, he was to me a father, a teacher, and a friend. He was a father to anyone who needed his guidance and he found the time to counsel all the young physicians, technicians, and clerks who sought his advice. He was a teacher to all who came to share his vast experience and knowledge of science and of life. He was a friend to those who sought his friendship and even to those who did not. His personality was radiant and inspiring, and his ideals and principles, his compassion and guidance have enriched the lives and influenced the careers of many of us. Most of his students and associates reached high-ranking positions in the academic and professional world. He was proud of their accomplishments, for in part, they were his accomplishment. The laboratories were his world, his home, and his purpose. The care of patients was his utmost consideration—his research a dream and a hope to improve that care. And, to make the dream a reality, he developed a "research institute in miniature" with a multidisciplinary staff, which has certainly contributed to the scientific milieu and the academic atmosphere in which Beth Israel has evolved into a large healing and teaching center.

Dr. Antopol's imagination and creativity, and the unparalleled depth and range of his knowledge and interests, made him a Renaissance man in the 20th century. Many institutions and organizations sought his knowledge, experience, and leadership. He was Professor of Pathology at the Mount Sinai School of Medicine, Professor of Biology at New York University, consultant Pathologist at various hospitals, member of numerous professional societies, Chairman of the Committee on Alcoholism and Drug Abuse (Commission on Public Health and Education), member of the Advisory Board of LOBUND (University of Notre Dame), and member of the Editorial Board of this Journal, just to mention very few of the positions and offices he held.

William Antopol died, but part of the scientist and the man he was will live forever in our minds and in our souls. Those of us who had the privilege of being close to him will be guided by his principles, his ideals, and his philosophy.

Chryssanthos P. Chryssanthou, M.D.
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CHARLES K. FRIEDBERG, M.D.
1905–1972

In Memoriam

DR. CHARLES K. FRIEDBERG

1905–1972

July 14, 1972, a tragic accident deprived the Mount Sinai firmament of one of its brightest stars. Returning from a consultation at Albany Hospital—carried out for humanitarian reasons despite an overburdened schedule—Dr. Charles K. Friedberg succumbed in an automobile collision while at the apogee of his powers and with years of continued creative accomplishment ahead of him.

Dr. Friedberg worked his way through Columbia College and medical school by teaching mathematics and other subjects at night school. It is interesting, in light of his subsequent purely scientific career, that while in college he won the prestigious Chanler prize in history and the Einstein prize in American Diplomacy. Following graduation from the College of Physicians and Surgeons of Columbia University and internship at Mount Sinai Hospital, he worked in physiologic and pharmacologic laboratories in Vienna and Amsterdam. Returning to the United States in 1932, his entire subsequent career was passed at The Mount Sinai Hospital. From the start, he worked both in the laboratories and the clinical services, while at the same time maintaining a private practice. The diversity of his original investigative work is remarkable: pathological anatomy, bacteriology, biochemistry, experimental pathology, and manifold aspects of clinical cardiology.

Dr. Friedberg's earliest investigations at Mount Sinai were carried out with Louis Gross and were concerned with the pathologic anatomy of the heart in rheumatic fever and disseminated lupus erythematosus. He worked on bacterial endocarditis with Emanuel Libman; they published a monograph on the subject which was the standard work at the time. He stressed the need for prompt, intensive antibiotic treatment in subacute bacterial endocarditis without waiting for positive cultures.

The breadth of Dr. Friedberg's activities in cardiology made clear to him, during the forties, the need for a comprehensive monograph encompassing the tremendous recent advances in cardiology. Only one who had worked in the field experimentally, anatomically, and, above all, clinically, could even have ventured single-handedly on this Herculean task. When *Diseases of the Heart* appeared in 1949, it was immediately and universally hailed as the "cardiac bible." It has remained a world standard. Translations have appeared in French, German, Spanish, Italian, Greek, and Japanese. There is even a pirated edition circulating in Asia. The status of Dr. Friedberg's book is aptly characterized in a review of a book on clinical cardiology in the current issue of the *Journal of the American Medical Association* (July 17, 1972): "For cardiology, Dr. Friedberg's conspicuous success in maintaining uniform excellence while covering the entire field provides the stratospheric standard against which other single-authored texts can continue to be judged."

For many years, Dr. Friedberg directed the cardiology laboratories and clinical cardiological services at The Mount Sinai Hospital and Mount Sinai School of Medicine. The annual postgraduate course in cardiology which he inaugurated and conducted at Mount Sinai for the American College of Physicians quickly became so popular that attendance had to be limited. An entire generation of cardiologists grew up under his tutelage.

Dr. Friedberg founded and edited the distinguished series of monographs "Progress in Cardiovascular Disease." In 1970, he became editor-in-Chief of *Circulation*, the official journal of the American Heart Association.

All these activities were carried out productively while conducting an extensive and widespread consultation practice. This would hardly have been feasible without the active participation of his wife Gertrude, playwright, author, and teacher of mathematics. Especially in the manifold editorial activities associated with the writing of *Diseases of the Heart*, they worked as a team; the results speak for themselves.

The Mount Sinai Medical Center and American medicine are the poorer for the tragedy of July 14.

ARTHUR M. FISHBERG
for the
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Effects of a Liberalized Abortion Law in New York City

JEAN PAKTER, M.D., M.P.H.* AND FRIEDA G. NELSON, B.A.†

Over 250,000 abortions have been performed in New York City from July 1970 to December 1971 under the law which permits abortion with the consent of the mother and her physician up to 24 weeks of gestation. Of these 250,000, 65 percent were for nonresidents. The trend for abortions for nonresidents has been steadily increasing in numbers and proportions from under 55 percent for the first six months of the abortion program to over 67 percent in the last six months. Abortions to residents, although increasing in number, showed a decline in the percentage of total abortions during these 18 months. The characteristics of residents and nonresidents show some differences.

Providers of Abortion Services

The residents of the city utilize municipal and voluntary hospitals chiefly for their terminations of pregnancy. However, in recent months residents are utilizing free standing clinics somewhat more than previously, indeed more than the ward or private services of voluntary hospitals and more than the proprietary hospitals.

For the nonresidents, the shift from hospital utilization to free standing clinics took place relatively early and has increased rapidly. The result is that over 55 percent of all abortions on nonresidents are performed in the free standing clinics. Thus, the free standing clinics have emerged as major providers of abortion services for nonresidents, followed by the proprietary hospitals.

Stage of Pregnancy at Termination

In the beginning, over 30 percent of the residents were getting abortions in the later period of gestation, i.e., 13 weeks or over. As time has progressed, proportionately more are appearing earlier, and currently about 80 percent are coming in during the first trimester. However, nonresidents had tended to come in earlier than the residents when the program got underway; but now the two categories are on a par as far as stage of pregnancy at termination is concerned.

Method of Termination

The most popular method of termination has become increasingly suction-curettage. In the beginning D & C was used more frequently but now this

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TABLE I

Total Number and Percent of Induced Abortions in New York City by Method of Termination and Provider

July 1, 1970–December 31, 1971

Provider	Numbers					Percents				
	Method of termination					Method of termination				
	Total	D & C	Suction	Saline	Hysterotomy	Total	D & C	Suction	Saline	Hysterotomy
Municipal	31,945	7,430	15,639	8,361	515	100.0	23.2	49.0	26.2	1.6
Voluntary—Service	14,273	3,588	7,366	3,070	249	100.0	25.1	51.6	21.5	1.8
Voluntary—Private	35,552	11,361	17,067	6,564	560	100.0	32.0	48.0	18.4	1.6
Proprietary	80,360	32,897	29,704	17,327	432	100.0	40.9	37.0	21.6	0.5
Free Standing Clinics	88,502	6,721	81,588	184	9	100.0	7.6	92.2	0.2	0.0*
Total	250,632	61,997	151,364	35,506	1,765	100.0	24.7	60.4	14.2	0.7

* Less than 0.05.

procedure has been utilized much less in favor of suction, which mode has been employed for about 60 percent of all abortions (resident and nonresident) (Table I).

The saline induction method reserved for late terminations accounted for almost 20 percent of abortions for residents and 13 percent for nonresidents at first. Since residents have begun to appear earlier in their pregnancies, the proportion of saline termination has dropped to 13 percent for them too.

Racial Distribution

The nonresidents coming to New York have been predominantly white—about 88 percent. The nonresident Blacks seeking abortions have recently shown a slight increase to 12 percent.

Among the residents, all racial and ethnic groups are represented; the distribution is 45 percent white, 44 percent nonwhite and 11 percent Puerto Rican. When these percentages are compared to births, it is evident that legal abortions are being sought by all socio-economic and ethnic groups now that these services have been made available (Table II).

Age Distribution

A review of the age distribution of women getting abortions shows that the proportion of those 17 years of age or less is increasing somewhat both for residents and nonresidents. For the residents, the proportion has risen gradually from 5 percent to 7 percent, and for nonresidents it has risen from less than 10 percent to over 12 percent. Teenagers through 19 years of age accounted for approximately 17 percent of abortions to residents, but comprised almost one third of all nonresidents (Table III).

TABLE II

*Number and Percent of Induced Abortions and Live Births and Ratios of Abortions to Live Births to New York City Residents by Race and Ethnic Group**

July 1, 1970–June 30, 1971

Race and Ethnic Group	Abortions			Live Births		Ratio of Abortions per 1,000 Live Births
	Number	Estimated total number	Per-cent	Number	Percent	
White	23,927	29,428	47.0	73,333	54.2	401.3
Nonwhite	21,770	26,772	42.7	40,049	29.6	668.5
Puerto Rican	5,222	6,425	10.3	21,919	16.2	213.1
Total	50,919	62,625	100.0	135,301	100.0	462.9

* Source: Certificate of termination of birth certificates.

TABLE III

*Number and Percent of Induced Abortions in New York City to Residents and Nonresidents by Age of Women**

July 1, 1970–December 31, 1971

Age of Women	Numbers			Percents		
	Total	Residents	Non-residents	Total	Residents	Non-residents
17 or less	24,164	5,395	18,769	9.6	6.2	11.5
18-19	41,549	9,161	32,388	16.6	10.6	19.7
20-29	134,633	50,551	84,082	53.7	58.5	51.2
30-34	26,778	12,122	14,656	10.7	14.1	8.9
35 & over	22,351	8,715	13,636	8.9	10.1	8.3
Not Stated	1,157	437	720	0.5	0.5	0.4
Total	250,632	86,381	164,251	100.0	100.0	100.0

* Source: Certificate of termination of birth certificates.

Previous Pregnancies

At the outset, among residents seeking abortion, 46 percent were primiparae; and, among the nonresident group, 68 percent were primiparae. As time has elapsed, the proportion of primiparae for both groups appears to have decreased slightly.

Almost 23 percent of residents and 14 percent of nonresidents had histories of three or more previous term pregnancies. Clearly, this finding would indicate that abortions are sought not only by young women not ready to accept responsibility of motherhood for the first time but by women who feel a need to curtail the size of their family. This is even more evident for the residents of the city than for the nonresidents.

TABLE IV

*Complications Following Abortion, by Type and Period of Gestation, Number and Rate per 1,000 Abortions—New York City**

July 1, 1970–December 31, 1971

Type of Complication	Total		12 Weeks and Under		13 Weeks and Over	
	Number	Rate	Number	Rate	Number	Rate
Hemorrhage	252	1.1	112	0.6	140	3.5
Infection	329	1.5	153	0.8	176	4.5
Perforated Uterus	298	1.3	246	1.3	52	1.3
Anesthesia	18	0.1	13	0.1	5	0.1
Shock	10	†	2	†	8	0.2
Retained Tissue	520	2.3	87	0.1	433	11.0
Failure	78	0.3	7	*	71	1.8
Lacerated Cervix	49	0.2	41	0.2	8	0.2
Other	89	0.4	49	0.3	40	1.0
Unspecified	14	0.1	9	*	5	0.1
Total Complications	1657	7.3	719	3.8	938	23.7
Total Abortions	226,722		187,099		39,623	

* Source: Weekly Abortion Reports.

† Less than 0.05.

Complications

Terminations over 12 weeks of gestation carry a much higher complication rate —23.7 per 1000 compared with 3.8 per 1000 for this of 12 weeks gestation or less (Table IV). The most common complication reported for terminations 12 weeks or less was perforation of the uterus, reported as 1.3 per 1000. Infection and hemorrhage follow.

The complication rates appear to be declining as a trend, but the higher ratio of complications among late terminations compared to early terminations persists. From the data it is clear that the hazards of complications following D & C or suction increase when these are associated with terminations over 12 weeks. Perforation of the uterus following D & C was four times more likely and, following suction, more than ten times more likely, when these procedures were attempted after the first trimester.

Saline terminations compared to suction carry 7.6 times the rate of complications but when compared to D & C the rate is 5.5 times greater (for all gestations) for the entire 18 months. Retained tissue is the most frequently reported complication (Table V).

Mortality

From July 1, 1970 to December 31, 1971, 12 deaths occurred following legal abortions in New York City. Of these, eight occurred in the first twelve months and 4 in the following six months. Based on the number of abortions performed,

TABLE V

*Complication Rates per 1000 Abortions by Type and Method of Termination, New York City**

July 1, 1970–December 31, 1971

Type of Complication	Total	Methods of Termination				
		Dilation and curettage	Suction	Saline	Hysterotomy	Other including hysterectomy
Hemorrhage	1.1	1.0	0.5	4.0	3.7	0.9
Infection	1.5	0.9	0.8	5.4	11.0	1.5
Perforated Uterus	1.3	1.9	1.3	0.2	5.1	2.1
Anesthesia	0.1	0.1	0.1	0.1	0.7	—
Shock	*	*	*	0.2	0.7	
Retained Tissue	2.3	0.5	0.5	14.7	1.5	0.6
Failure	0.3	*	*	2.4	—	—
Lacerated Cervix	0.2	0.3	0.2	0.1	0.7	0.3
Other	0.4	0.3	0.3	1.0	4.4	0.6
Unspecified	0.1	0.1	*	0.2	—	0.6
Total	7.3	5.1	3.7	28.3	27.8	6.6

* Source: Weekly Abortion Reports.

the fatality rates were 4.7 per 100,000 abortions and 3.7 per 100,000 for these two periods respectively (Table VI).

For abortions performed at 12 weeks or less gestation, the abortion mortality rate was 2.2 per 100,000 the first year and declined to 1.1 per 100,000 the succeeding six months (July to December 1971). For terminations over 12 weeks gestation, the abortion mortality rate was 16.9 per 100,000 the first year and 15.8 per 100,000 the next six months.

Of the 12 fatalities among the legally performed abortions, five followed saline terminations, four followed hysterotomy, two followed D & C, and one followed suction. Terminations performed by hysterotomy appeared to have the highest complication and fatality rate of all.

It is apparent that for terminations undertaken after 12 weeks gestation, the risk of mortality and morbidity rises and that methods employing saline and/or hysterotomy carry much greater risks.

Experience to Date—Progress and Problems

Over a year and a half have elapsed since the liberalization of the New York State abortion law. At this time it is pertinent to review the trend in maternal mortality as well as data on admissions to hospitals for patients with sequelae following so-called "criminal" or illegal abortions.

In 1969 there were 77 maternal deaths, 24 of which followed illegal abortion at a rate of 5.3 deaths per 10,000 live births. The following year in 1970 the number of maternal deaths dropped to 68 with 22 abortion deaths at a rate of 4.6 deaths per 10,000 live births. By 1971 this number dropped to 38 of which 12

TABLE VI

*Abortion Mortality Rates by Length of Gestation and Method of Termination**

July 1, 1970–December 31, 1971

Numbers	Total 18 Months	July 1, 1970–June 30, 1971	July 1, 1971–Dec. 31, 1971
Length of Gestation			
12 Weeks and under	4	3	1
13 Weeks and over	8	5	3
Total	12	8	4
Method of Termination			
D & C	2	2	0
Suction	1	1	0
Saline	5	2	3
Hysterotomy	4	3	1
Total	12	8	4
Rates per 100,000 Abortions			
Length of Gestation			
12 Weeks and under	1.7	2.2	1.1
13 Weeks and over	16.5	16.9	15.8
Total	4.3	4.7	3.7
Method of Termination			
D & C	3.2	5.0	0.0
Suction	0.6	1.0	0.0
Saline	14.2	9.3	21.8
Hysterotomy	235.0	230.2	250.6
Total	4.3	4.7	3.7

* Source: Bureau of health statistics and analysis vital statistics certificates.

were abortion-associated deaths. Of these, seven were legally induced, three illegally or self-induced, and two "spontaneous" abortions (Fig. 1). Thus, a record-breaking low rate of 2.9 deaths per 10,000 live births was achieved, representing a decline in the rate by 37% from 1970 to 1971. Based on these figures, at least 40 women are alive today who would have lost their lives in the last 18 months because of attempted unskilled "criminal type" abortions.

In municipal hospitals and voluntary hospitals which admitted many of these patients in septic shock or hemorrhaging, the numbers of such admissions have declined dramatically. For example, in one of the municipal hospitals which had over 1000 in 1965, the number declined to about 300 in 1971. This means saving of lives, saving of expensive and intensive hospital care and fewer disrupted homes because of a woman's serious illness.

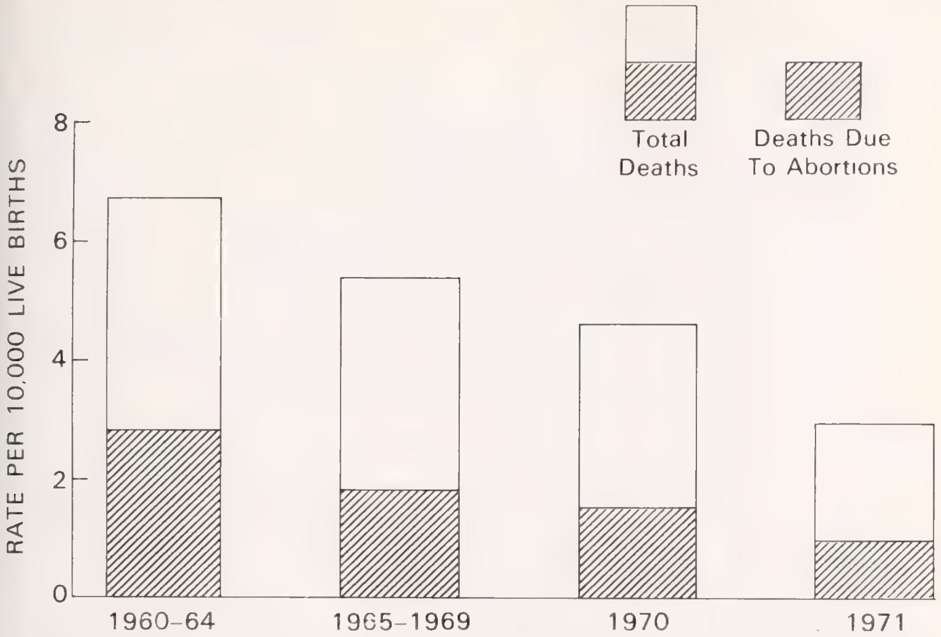

FIG. 1. Pregnancy-associated deaths: total deaths and those due to abortions. Rate per 10,000 live births, New York City, 1960–71.

The trend in births and birth rates also has shown the impact of the liberalized abortion program. From 1970 to 1971 the births in New York City dropped by 11.6 percent, whereas the national decline in births was 4.3 percent for this period (Fig. 2). It was also observed in the course of the year that the birth rate was declining at an accelerating pace in the city.

Concomitant with the decline in all births in New York City for the first time since data were collected on out-of-wedlock births i.e., for almost two decades, a decrease in out-of-wedlock births was also noted in 1971. In fact a numerical decrease of 3777 was recorded for 1971, compared to 1970, which was a decline of 11.8 percent. The shelters for unwed mothers have all reported a dramatic decline in the number of young women requesting shelter care. This, in turn, has led to a drop in numbers of babies up for adoption.

Since out-of-wedlock births have been associated with much higher rates of premature birth and, indeed, infant mortality, the decrease in out-of-wedlock births undoubtedly exerted a favorable influence on infant survival. Those factors as well as others have indeed been influential in the achievement also of a record low in infant mortality which dropped to 20.7 deaths per 1000 live births in 1971. The decline was entirely in the neonatal (first 28 days of life) period. Evidently the curtailment of unwanted pregnancies has been of benefit. Such an effort was indeed hypothesized. In many of the European countries where much lower infant death rates prevailed than in the USA, a tradition of liberalized legal abortions has existed for many years.

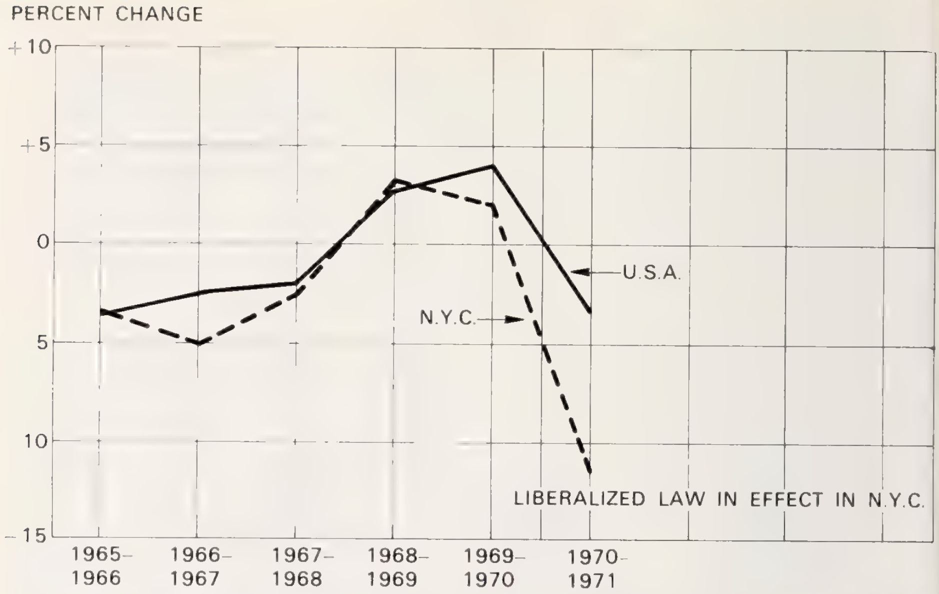

FIG. 2. Annual percent change in the number of live births: United States and New York City, 1965 through 1971.

As of this date it can be stated that the liberalized abortion program in New York City has been associated with a dramatic record breaking decline in maternal and infant mortality. Hopefully, as knowledge of genetics and counseling is expanded, it can be anticipated that births of damaged and hopelessly defective fetuses can be minimized.

So much then for the positive aspects of the program. What are our concerns and what may be the problems? We are concerned that unethical entrepreneurs and commerically motivated individuals may adversely affect standards of good care. Accordingly, it is a public health responsibility in conjunction with the medical profession's support to ensure that abortions are performed in substantial compliance with the regulations.

Although commercial referral services have been outlawed in New York City, their existence is still felt and their unethical practices persist, particularly outside New York City and linked with certain facilities in the city.

Fetuses showing signs of life at time of expulsion are relatively rare and usually do not survive more than a few minutes. However, even though the occurrence is rare (62 out of 200,000 abortions) it is none the less disturbing to all concerned. There has been much misquotation in the press about this. To set the record straight, two have survived; but these were well beyond the 24th week period of gestation. Clearly, unless there is a compelling medical reason, physicians should make every effort to limit terminations over 20 weeks gestation.

As time elapses, we note that about 3000 women have had repeat abortions since July 1, 1970. Although this represents a small proportion of the total, nevertheless it would indicate the need for adequate counseling of patients regarding effective contraception.

Finally, we must inculcate an increased sense of responsibility in men as well as in women to adopt and maintain reliable pregnancy control methods to avoid the necessity of abortions for curbing pregnancy.

Until newer developments materialize, our present approaches to abortion are essentially surgical and not entirely free of risk as is even the simplest surgical procedure, particularly where anesthesia is administered.

Answers are not available yet as to the percent of women who may develop infertility as a sequel of an abortion. Nor do we know what the future competence of child-bearing will be in a women who has had several abortions or even one if cervical lacerations or uterine perforation has occurred.

A national approach for all states to repeal or liberalize abortion laws is essential. For women to have to travel hundreds of miles to seek an abortion in New York City is not only inhumane, adding to her risks and costs, but fosters discrimination against the poor since only those with funds can afford to come to New York City.

Summary

All the evidence to date indicates that on balance our liberalized abortion law has achieved enormous good in decreasing morbidity and fatalities due to "criminal" or illegal abortions, a record-breaking decline in maternal deaths, a decrease in out-of-wedlock births and a decline in infant deaths. With all it has imparted a responsibility to keep our goals clearly in sight and maintain a perspective of achieving effective fertility control which would minimize the need for abortions.

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An Inflatable System for Intracavitary Treatment of Cancer of the Uterine Cervix

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We have designed an inflatable system for use in the treatment of cancer of the uterine cervix with radioactive material. Intracavitary radiation has been an established treatment of choice for carcinoma of the cervix of the uterus for scores of years. In general, the devices for intracavitary treatment comprise an intrauterine tube or tandem and an intravaginal component or colpostat. Many workable variations of this arrangement are available. These systems are of two types, fixed and loose. The prototype fixed systems are the Ernst (1), Fletcher–Suit (2), and Henschke (3) devices in which the tandem is fixed to the colpostat. A loose system has no fixed connection between the tandem and the vaginal component, and this type is characterized by the Manchester and Paris systems.

Our radiation research laboratory has developed a miniaturized system for afterloading the uterine cavity with multiple irradiators for the treatment of endometrial carcinoma (4, 5), and we have adapted this system to the treatment of cancer of the cervix of the uterus with a fixed system.

When we insert multiple bulbous-ended tubes (afterloading Heyman applicators) in the uterine cavity for the treatment of endometrial cancer, we find that the thin plastic tubing is conveniently packed and held in the vagina by an inflatable rubber doughnut through which the tubing is inserted. The practical success of this form of vaginal packing for the treatment of cancer of the endometrium has led us to adapt the inflatable doughnut principle in the design of our inflatable cervix system.

Our miniaturized sources, using cesium 137 as the substitute for radium, make our system more flexible, simpler, more easily inserted, and more adaptable to distortions of anatomy than existing systems (Fig. 1).

The tandem or intrauterine tube is attached to the vaginal component or colpostat. The tandem in this prototype device is 6 cm in length and 3 mm in outer diameter. The outer diameter of 3 mm was selected because it is the diameter of the uterine sound conventionally employed to probe the uterine cavity before the insertion of any intrauterine device. Also, a 3 mm diameter tube can be inserted without anesthesia, general or local. The material is silicone-coated, polyvinyl chloride plastic sufficiently rigid to be inserted into the uterine cavity, but flexible enough to accommodate most uterine positions.

Attached to the tandem, and molded with it in manufacture, is a PVC inflatable barrel shaped bag, concave at the position of attachment of the tandem on one end of the barrel. This concavity allows the cervix to nestle into the top of the cylinder. In the forniceal end of the barrel there are hemicylinders adherent to the PVC wall so that their rounded surfaces will be located

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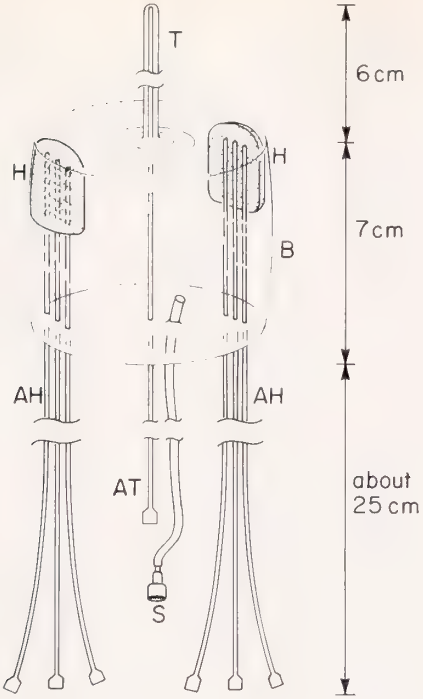

Code:
T = tandem or intrauterine tube, 6 cm long, 3 mm outer diam.
B = inflatable polyvinyl chloride bag.
H = hemicylinder, 2 cm in height, 2 cm diam, adherent to interior surface of PVC bag (B).
AH = afterloading tube to vaginal hemicylinder which fits in vaginal fornix; 3 such tubes extend into each hemicylinder for variable loading.
AT = afterloading tube to tandem in the uterine cavity.
S = connection for syringe to inject air or fluid into bag after device is inserted into uterus and vagina.

FIG. 1. Diagram of Inflatable Cervix System

laterally in each fornix, while their flat surfaces face each other. The hemicylinders lie in the axis of the vagina, and when the bag is deflated these hemicylinders can be brought together to minimize the diameter of the device at the time of insertion.

The barrel-shaped bag of PVC is inflatable, measures 6 cm in diameter and 7 cm in length, and is designed to distend and fill the vagina.

Plastic tubing leads from the tandem and from the hemicylinders to allow afterloading with radioactive material. The plastic tubing is identical in dimensions to the tubing in our afterloading multiple irradiators of the Heyman type for the intracavitary packing of cancer of the endometrium. Thus, the same radiation sources of ^{137}Cs can be used in the treatment of cancer of the cervix as we have used for several years in the treatment of carcinoma of the endometrium.

When the patient is ready for treatment she is placed on a gynecologic examining table and the cervix exposed with spades. A tenaculum is placed on the anterior lip of the cervix. A uterine sound is inserted to ascertain the size and direction of the cavity. The deflated cervix system is held by the trailing afterloading plastic tubes, and the tandem portion is inserted into the uterine cavity for its complete length of 6 cm. Then the PVC bag is inflated to its capacity with about 60 ml of air or liquid containing a small amount of radiopaque material and a blue dye. The hemicylinders in the fornix are oriented laterally by grasping the 3 tubes issuing from each of these hemicylinders and using them to rotate the bag into proper position. The plastic tubes in the cervix system contain dummy steel wires of the same dimensions as the carriers of the subsequently loaded radioactive material. There is no need for additional packing of the vagina, for the inflated barrel-shaped bag retains the tandem in the uterine cavity and keeps the hemicylindrical vaginal source holders in each fornix. A Foley catheter is inserted in the bladder for the duration of the treatment.

Before the device is loaded with radioactive material, x-ray films are made to locate its exact position, and the components can be related to the tumor by proper marking of the cervix and tumor with silver clips.

There will be a standard form of loading with 60 mgm of radium-equivalent ^{137}Cs in the tandem, and 10, 20, or 30 mgm of radium-equivalent ^{137}Cs in the hemicylinders as desired and as indicated by the tumor.

The radioactive material is inserted only after all handling of the patient by personnel, when the patient is finally in her own room. The loading is done essentially as at present in the afterloading of cancer of the endometrium, and the exposure to personnel is minimal (6, 7).

This system has several advantages over currently used devices. Its prototype is the system devised by Pierquin and Chassagne (8) of the Gustave-Roussy Hospital in Paris, where each patient has a custom-made, shell-like plastic mould into which tubes are inserted for subsequent loading with radioactive cesium. Although that custom-made method is considered excellent, it requires too much sophistication to be used as a practical method of treating cancer of the cervix of the uterus, and it has not been universally adopted. The system we describe is somewhat less rigid than the one used in the Gustave-Roussy Hospital. The simplicity of our device makes it possible to use it anywhere as long as the miniaturized sources of ^{137}Cs we have previously described are available.

It is unnecessary to anesthetize the patient for introduction of this device, thus sparing the economic burden of the use of an operating room. The device is disposable, although economic necessity could make it reusable. The alignment of three separate plastic afterloading tubes in each forniceal hemicylinder makes it possible to spare the bladder or the rectum or both, or even to concentrate the radiation on one side or the other by loading the hemicylinders asymmetrically. Dosimetry of such an attached system is demonstrated by computer, and loading can be adjusted to suit variations in anatomy or site of disease. Another attractive feature of this inflatable cervix system is its adaptability for use where medical facilities may be meager, in developing areas, and, of course, here in the United States.

Summary

An inflatable plastic barrel-shaped bag containing hemicylinders in each fornix can be used as a vaginal applicator for carrying radioactive materials. Fixed to the bag is a tandem for intrauterine treatment. This system contains plastic tubes which allow afterloading radioactive material into the cervix system. It is simple and flexible. The same miniaturized radioactive sources which have been developed and found useful in this hospital for the treatment of endometrial carcinoma are used in this system.

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Immunotherapy of Human Leukemia

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Introduction

Although significant advances have been made in the treatment of childhood acute leukemia, chemotherapy for the majority of adults with acute and chronic leukemias remains largely palliative. Recently interest has been revived in manipulation of immune mechanisms as a treatment modality complementary to chemotherapy. It is hoped that by manipulation of host responses to tumor antigens, patients will be made to reject their tumors in much the same way that they would reject other foreign material and in a more specific fashion than is now possible with chemotherapy. Most importantly, the immunologic approach may allow the development of methods to prevent the onset of tumors by the use of vaccines.

In the last ten years, there has been a large number of studies of immune mechanisms to control tumor growth with increasing attention being paid to the role of immunotherapy in human leukemia. Several excellent reviews are now available dealing with the search for tumor-specific antigens with some reference made to trials of immunotherapy in man (1–5). This paper is intended to review the recent literature on trials of immunotherapy for human leukemia.

I. *Tumor-Specific Antigens and Host Response*

The rationale of immunotherapy is based on the existence of antigens specific to the tumor but not to normal tissues, the evidence for which is reviewed extensively elsewhere (1). Tumor-related antigens occur both inside the cell and on the cell surface, but it is surface antigens that are accessible to host-immune defenses. Antigens present on the cell surface of tumor cells that are capable of inducing host rejection responses in autochthonous and/or syngeneic hosts are called tumor specific transplantation antigens (TSTA) (1, 6).

Tumor-specific transplantation antigens in animal tumors have been well defined by transplantation experiments in inbred strains and by serologic investigations in vitro (2). In animal systems those tumors induced by chemical carcinogens have antigens distinct to each individual tumor, whereas those induced by viruses have antigens shared by other tumors induced by the same virus. Some tumors induced by RNA viruses have antigens shared with tumors induced by other RNA viruses, notably within the Rauscher, Friend, and Maloney group (2, 7).

The host response to transplanted tumors in syngeneic animals is similar to other transplantation responses and involves both cellular and humoral immunity, including the anamnestic response characteristic of immunologic memory

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(2). The cell-mediated mechanism is generally more efficient in initiating effective cytodestruction than known antibody-mediated mechanisms, and, in fact, serum antibodies may be associated with enhancement of tumor growth (3, 6). Tumors induced by RNA viruses are more susceptible than others to the cytotoxic effect of antibodies and complement (2).

In human work, evidence for TSTA must necessarily be indirect since transplantation experiments are precluded by ethical considerations, but TSTA have been demonstrated in human leukemia, by serologic methods and by demonstration of cellular host responses.

Garb, Stein, and Sims produced antisera to leukemic cells in rabbits that had received repeated neonatal injections of normal human leukocytes. In most cases antisera from these rabbits showed precipitin reactions with extracts of buffy coat from leukemic patients and less often with normal leukocytes (8). Hyde et al produced antisera to human myeloid leukemia cells in rabbits previously given repeated neonatal injections of normal human leukocytes. After absorption with the normal cells these antisera reacted specifically with myeloid but not with lymphoid leukemia cells nor with normal leukocytes (9). Yata et al prepared an antiserum against human leukemic cell homogenate in rabbits previously rendered tolerant by injections of normal leukocytes from several donors. The antiserum showed specificity for many leukemia and lymphoma tissue extracts but also reacted strongly with normal thymus and other lymphoid extracts (10). Viza et al prepared antisera against the papain-solubilized surface antigens of leukemia cells; after extensive treatment with normal human serum, soluble HL-A antigens and papain, preliminary studies suggested that the treated sera reacted in vitro with leukemic but not with normal cells (11). Mann et al produced antisera in rabbits against cultured Burkitt lymphoma cells and absorbed these sera repeatedly with normal human leukocytes; the antisera then reacted with cells from patients with myeloid and lymphoid leukemia, but not with normal leukocytes (12). Gold and Freedman point out that radioiodinated tumor-specific antibodies are removed or inactivated by repeated absorption with antigenically similar but not identical cell lines; they found some cross-reactions between normal and neoplastic leukocytes and none of their reagents reacted selectively with all leukemia cells (14).

We have recently described a method of producing antisera to leukemic cells in mice rendered tolerant to the same patient's remission leukocytes (15).

Cellular reactivity to human leukemia has been demonstrated both in vivo and in vitro. The delayed hypersensitivity response to skin test antigens is perhaps the best test of cellular immunity, and patients with acute leukemia (16) have developed delayed hypersensitivity to cutaneous injections of autologous tumor extracts with some suggestion that a positive skin test correlates with improved prognosis. Lymphocyte transformation in vitro using intact tumor cells or cell extracts as the stimulating antigen has also been demonstrated in patients with leukemia (17–19).

Although evidence in humans is necessarily indirect, the existence of leukemia associated antigens and a significant host response to these antigens is strongly suspected.

II. Immunotherapy in Animal Models

The term "immunotherapy" refers to attempts to initiate or augment an immunologic reaction against tumor antigens. Treatments may involve induction of active immunity in which the host's own immune mechanisms take part in the reaction, or passive immunity in which exogenous immunocompetent cells or antibodies are given. In a third type of therapy, immunologic adjuvants are employed which act to increase an immunologic response when mixed or combined with a tumor antigen.

Immunotherapy in animal models has been successful in suppressing growth of established tumors and in preventing growth of transplanted tumors. Maneuvers employing the principles of active and passive immunization as well as immunologic adjuvants have all been shown to have some effect, although generally the size of tumor being treated must be quite small. The availability of highly inbred animal strains and of tumors known to share antigens has been an advantage in animal work not usually applicable to human clinical studies.

Immunologic adjuvants have been known for some time to be able to increase host responsiveness to antigenic challenge. Certain adjuvants such as Freund's complete adjuvant (a water-in-oil emulsion with added Mycobacteria) are particularly effective in enhancing delayed-type hypersensitivity by mechanisms as yet unknown (20). Since cell-mediated immunity is apparently a better defense against tumor growth than antibody formation (21), adjuvants of this nature could be expected to improve host defenses if injected in the presence of tumor antigens.

Old et al (22) in a definitive study of the reaction of the reticuloendothelial system to neoplasia showed that Bacillus Calmette-Guerin (BCG) injections could enhance the reaction against tumor specific antigens and extend the latent period of sarcoma induction by methylcholanthrene. The growth of tumor grafts within syngeneic strains was not affected. BCG has also increased resistance to growth of transplanted polyoma tumors (23) and L1210 leukemia (24) in mice. A killed suspension of Corynebacterium parvum has been used to retard growth of syngeneic mammary tumors (25), transplanted mouse sarcomas (26), and murine fibrosarcomas (27).

The most promising results in the prevention and treatment of animal tumors come from studies in which active immunity has been induced to tumor cells or viruses. Evans et al (28) have studied antitumor immunity in the Shope papilloma-carcinoma complex of rabbits, and have shown that autologous grafts consisting of intact papilloma cells increased the rate of complete regression of Shope papillomas, whereas homogenates, disrupted cells, or grafts of nontumor tissue did not. Eddy et al (29) administered homologous virus during the latent period to hamsters inoculated neonatally with SV40 or adenovirus and reduced the incidence of tumors as compared to controls receiving only a single inoculation of virus.

Haddow and Alexander (30) and Haddow (31) working with primary chemically induced fibrosarcomata in the rat showed that autografting of viable tumor tissue obtained by biopsy caused a temporary regression of the sarcomata but that this was an infrequent phenomenon. Oettgen et al (32) have transplanted subcutaneous sarcomas, too small to grow, into guinea pigs. This rendered the animals resistant to large tumor inocula up to 100 times the amount usually necessary for engraftment of tumor. Wespick et al (33) injected guinea pigs with living ascites tumor cells and protected them against intramuscularly injected tumors. Of interest is the finding that X-irradiated cells did not protect the animals, and that protection in all cases was only effective when the tumor dosage was small. Natale et al (34), on the other hand, found that fresh tumor cells irradiated with 10,000 to 100,000 R induced active immunity to transplanted methylcholanthrene tumors in C57BL/6 mice.

Mathe et al (35) established that immune rejection of L1210 leukemia cells could be effected in mice even if the immunizing dose was given several days after the infecting dose. Parr (36) and Morton (37) have also prevented tumor growth by giving immunotherapy after tumor induction. The importance of this observation lies in its analogy to human tumors which are well established prior to the onset of therapy; however, the tumor dose given to these animals must still be quite small.

Impressive results have been obtained in the treatment of established solid tumors by induction of active immunity with tumor cells treated with neuraminidase (38), an enzyme which removes sialic acid residues from the cell membrane and causes several changes in membrane-related cell functions (39). Tumor cells such as Landschutz ascites tumors (40), L1210 leukemia (41, 42), and methylcholanthrene-induced sarcoma cells (43, 44) exhibit increased antigenicity when treated with neuraminidase and as a result grow less well in hosts that are normally susceptible. Simmons and Rios (45) have now shown that firmly established methylcholanthrene fibrosarcomas in mice may regress and disappear completely when the host is immunized with Vibrio cholera neuraminidase-treated autochthonous tumor cells.

Adoptive or passive cellular immunotherapy of animal tumors has largely been shown to retard rather than prevent growth of tumors. Woodruff et al (46, 47) initially showed that heterologous cells from rat spleen or thoracic duct were more effective in retarding tumor growth in mice when the donor rats were previously immunized with mouse tumor cells. Delorme and Alexander (48) used both syngeneic and allogeneic immune lymphocytes to treat rat fibrosarcomas and also noted retardation of growth. Alexander et al (49) further reported that allogeneic spleen cells prevented growth of L5178Y leukemia in DBA/2 mice if the donors were immunized with leukemia cells but not with normal DBA/2 cells.

Nucleic acids extracted from sensitized lymphocytes have been effective in transferring passive immunity either by injection directly into the recipient (50) or by injection of the spleen cells that were first incubated with these nucleic acids (51).

Immunotherapy with passively transferred antisera has met with variable success in different systems. Gorer and Amos (52) first showed that antibody could influence tumor growth in histocompatible CBA mice, but Evans et al (28) could not prevent growth of Shope papillomas in rabbits using serum from animals with spontaneously regressing tumors. Old et al (53) immunized rats with rat leukemias carrying the Gross virus thus making antibody against G+ cells but not hetero- or isoantibodies. The rat antiserum completely protected mice against challenge with G+ mouse leukemia cells when given up to three days after inoculation of challenge cells.

Passive immunotherapy has met with variable success in Friend leukemia of mice (54), murine sarcoma (55–57), and human lymphomas serially transplanted in hamsters (58). Enhancement phenomena may occur in the presence of antitumor antibodies but this may be important only with small quantities of antibody (59). The problems related to enhancement are discussed in other recent reviews (60, 61).

Prevention of tumor growth in animal models by immunologic means is quite successful and in a few systems regression of established tumors can be effected. These developments have encouraged investigators to continue with trials of immunotherapy for human leukemias and other malignancies.

III. Adjuvant Therapy

Nonspecific stimulation of the reticuloendothelial system by injection of foreign materials has been shown to enhance immune responsiveness in animal models, and has caused increased immunologic resistance to transplanted animal tumors, as reviewed above. It is a long-standing clinical observation that remissions in malignant disease have been associated with intercurrent infections (62). In most cases the infections were bacterial and largely pyogenic, but recently viral infections have also been implicated (63, 64).

These observations prompted early attempts at adjuvant immunotherapy using mixed bacterial toxins (65) and a recent monograph lists case reports of apparently beneficial effects of the use of these toxins on the course of human leukemia (66).

The most widely used adjuvant in human work currently is BCG vaccine. Davignon et al (67, 68) have reported that BCG vaccination given for prophylaxis of tuberculosis was associated with a diminished incidence of death from leukemia in a population reviewed in Canada. This was supported by data from England (69) but questioned by others (70–73). Similar studies in the United States and Scotland have failed to show a difference in leukemia mortality in patients with BCG (74, 75).

Mathe et al (76) used BCG alone to maintain remission in 8 patients with ALL and reported that five patients remained in remission for over 90 days. Longer remissions, however, occurred when active immunotherapy was also used. Willoughby (77) has similarly reported the use of weekly intradermal BCG therapy in acute leukemia with promising results but does not as yet state the number of patients so treated. Crowther et al (78) reported no difference between BCG and cytotoxic chemotherapy in maintenance of remission of six patients with acute leukemia. The leukemia committee of the Medical Research Council (79) has recently reported in a controlled series that patients with acute leukemia treated with BCG survived only slightly longer than untreated patients in a drug-induced remission. However, a different vaccination method and different BCG strains were used than in Mathe's study (76). Animal studies have also shown an apparent superiority of the Pasteur Institute BCG as an adjuvant (24).

BCG is a live attenuated bacillus and as such can cause disseminated disease particularly in an immunosuppressed host (80, 81). Local reactions at the vaccination site may also be severe (82, 83, 84) but are generally short-lived. The bacillus has usually been responsive to INH and other antituberculous drugs; however, fifteen deaths from generalized infection with BCG have been reported during the course of large scale prophylactic inoculations in Europe (80, 85). Thirteen of the earlier cases were presumed to have immune deficiencies, and the two recent cases were shown to be deficient in cellular immunity. Systemic infection with BCG has not been reported in patients with leukemia but the possibility of dissemination exists since these patients may have deficient cellular immunity (86).

Mathe et al (87) have also reported the use of a synthetic RNA analogue, Poly IC, as an immunologic adjuvant in patients with acute leukemia having less than 50 percent blasts in the bone marrow. Nineteen patients were treated and five had complete remissions of unstated duration. Guyer and Crowther (88) studied sixteen patients with acute lymphoblastic leukemia brought into remission with intensive chemotherapy. Half the patients were then treated with Bordetella pertussis vaccine 0.5 ml weekly or twice weekly by intramuscular injection. They concluded that immunotherapy possibly delayed the onset of relapse in the treated patients but no remissions longer than 455 days were obtained.

The use of BCG or other adjuvants in combination with active immunotherapy has led to better results than the use of BCG alone (76), and will be further discussed in the section on active immunotherapy.

IV. Active Immunotherapy

The principle of inoculating patients with tumor material was first explored by von Leyden in 1902, who repeatedly injected fluid expressed from autologous tumors into three patients with advanced cancers, two of whom seemed to improve (89, 90). In ensuing years a large number of studies were done using tumor cells or cell materials but generally indifferent results were obtained and enthusiasm waned (90, 91, 92). More recent studies have attempted to document host response to tumors as well as incidence of tumor regression or degree of prolongation of clinical remission. Inoculation of tumor materials have frequently been accompanied by steps designed to alter the antigenicity of the material or to improve the responsiveness of the host.

A great deal of interest was generated in active immunotherapy of human acute leukemia following early reports by Mathe et al that vaccinations with BCG or pooled irradiated human leukemic cells prolonged the duration of remission. In a recent series, Mathe (76, 82) presented studies on thirty patients, all with acute lymphoblastic leukemia in remission, but divided into several treatment groups for maintenance of remission. Eight patients received BCG vaccinations, five received injections of pooled irradiated leukemic cells, and seven received injections both of cells and BCG. Ten patients received no maintenance therapy and served as controls. The authors concluded that there was significant prolongation of remission in the group treated with immunotherapy regardless of the type of immunotherapy used. Six patients continued in remission for more than a year, four continued for more than two years, and one for more than three years. On further follow-up seven patients were in remission over two years, five patients were in remission over three years and two were in remission for more than four years (93). The authors stress that maximum reduction in the number of leukemic cells is essential and that no cytotoxic chemotherapy should be given during active immunotherapy. In support of this point, they have studied the effect of adding vincristine and adamantine to the active immunotherapy regimen of BCG and irradiated cells (94). By 500 days there was significantly better survival with the immunotherapy alone.

Southam (95) proposed that the most logical approach to cancer immunotherapy should include: treatment during a period of minimal residual disease; use of the patient's own cells as a source of tumor antigen; active immunization; and nonspecific stimulation of host defense mechanisms. He subsequently presented preliminary data on 12 patients with acute leukemia in remission treated with an autologous irradiated tumor cell vaccine. Patients were vaccinated at weekly intervals once in remission, using a preparation made from homogenized autologous leukemic cells stored at −70°C. The patients continued to receive cytotoxic chemotherapy when indicated. One of the twelve patients remained in remission longer than two years, and six out of nine had an increase in immediate skin reactivity to intradermal injection of leukemic cell extract.

Skurkovich (96) working in the U.S.S.R. has reported that twelve children with acute leukemia in relapse obtained clinical benefit from active immunization with allogeneic live leukemic cells. Leukemic peripheral blood cells and in some cases marrow cells were injected intravenously and intramuscularly for six to 28 days, followed by passive immunization with plasma and leukocytes obtained during a remission period. Five patients achieved a partial remission and three patients achieved a complete remission that was sustained up to six months at the time of reporting. Partial remissions were said to be easier to induce with cytotoxic agents.

Powles et al (97) removed and stored leukemia cells from the peripheral blood of nine patients with acute leukemia. When these patients were brought into remission with cytotoxic drugs, they were autoimmunized with the stored blasts. Although no report is made of clinical course, the leukemic cells were cultured with autologous lymphocytes both before and after the patients had been immunized with their own irradiated leukemic cells. All nine patients showed an increased stimulation of the patient's lymphocytes by autologous leukemia cells following autoimmunization. This system was proposed as a test for determining the best regimen for immunotherapy in acute leukemia.

Sokal et al (98) treated six patients with chronic myelogenous leukemia with BCG and cells from permanent culture obtained from the blood of patients with acute myelogenous leukemia. Regression of splenomegaly was noted and survival was better than eleven controls who did not receive immunotherapy.

Thornes et al (99) gave daily infusions of brinase, a proteolytic enzyme, to six patients with acute leukemia. The sera of these patients was cytotoxic to autologous blood cells including leukemic cells, and one patient treated with brinase alone achieved a clinical remission.

V. *Adoptive Immunotherapy*

Adoptive immunotherapy refers to a form of passive immunotherapy in which immunocompetent cells are transferred from donor to recipient. If the donor's cells take up residence and begin to reproduce in the recipient, the graft is said to "take." The graft may, however, attack the foreign antigens of its host, producing a characteristic and potentially lethal illness referred to simply as graft-versus-host disease (GVH).

Attempts at adoptive immunotherapy in humans have consisted of removing immunocompetent cells from the donor's bone marrow, peripheral blood, or spleen and transfusing these cells to recipients with malignant disease. The recipients have usually been conditioned prior to grafting with various treatments designed to increase graft acceptance, and in some cases the graft itself has been treated in vivo or in vitro to enhance its specific immunologic effectiveness.

Bone marrow transplantation has been used in patients with acute leukemia who have been previously treated with total body irradiation or massive doses of antitumor chemotherapy. In this situation the graft is expected to reconstitute normal marrow function that was damaged by aggressive therapy and to cause a controlled GVH reaction against any remaining host malignant cells. The optimal situation for this therapy would seem to obtain in identical twins, one of whom had contracted acute leukemia.

Thomas and others (100 102) initially reported three patients with acute leukemia treated with whole body irradiation followed by infusion of marrow from an identical twin. Although takes were obtained, the remissions were short-lived and the patients subsequently died. More recently Thomas's group (103) has treated four patients with refractory acute leukemia with 800 to 1,000 rads whole body irradiation and a bone marrow transplant from a normal identical twin. Once again the recipient's leukemia recurred within seven to twelve weeks. Subsequently an attempt was made to enhance the effectiveness of the marrow transplant by the use of additional immunotherapeutic procedures. Four additional patients were transplanted with isogenic marrow and subsequently received vaccination with autologous stored leukemic cells as well as buffy coat transfusions from the normal twin. Of the four patients treated, one achieved a remission of eight months' duration prior to relapse and one was continuing in remission after 13 months.

Transplants from donors other than identical twins (allografts) have also met with limited success but have the additional burden of GVH disease. Van Bekkum and DeVries (104) reviewed 60 bone marrow allografts in leukemic patients but stated that evaluation of reports was difficult since there were no controlled studies. Proof of marrow take was usually lacking or unconvincing and GVH disease was a frequent problem.

Mathe et al (105–108) attempted immunotherapy in 21 patients with acute leukemia by infusing allogeneic bone marrow into donors who had previously received whole body irradiation. In five patients the graft did not take, and the recipients died with bone marrow aplasia. Eleven patients, in whom the graft was successfully established, developed graft-versus-host disease and died of secondary syndrome. In four cases, the patients survived the secondary syndrome but eventually succumbed to their original leukemia or to infection within nine to twenty months after the bone marrow grafts.

The introduction and widespread use of human leukocyte typing has added a new dimension to bone marrow transplant attempts but has still made little difference in survival. Thomas et al (109, 110) have reported seven patients who were treated with bone marrow infusions from an HL-A matched sibling following 1,000 rads of whole body irradiation. Methotrexate was given to suppress GVH. Three patients with advanced leukemia showed histologic evidence suggestive of engraftment but the graft did not function and they died within 30 days. Four patients, three with acute lymphoblastic leukemia and one with Hodgkin's disease, showed evidence of a functioning marrow graft within three weeks. One patient died with graft-versus-host disease in 37 days; two patients died with recurrent leukemia after 85 and 102 days; and one patient continued to survive in remission after 200 days. One of the patients who developed recurrent leukemia was a girl who received male donor cells. Cytogenetic analysis of the leukemic cells unexpectedly revealed a male karyotype which has led to wide speculation about the nature of leukemic relapse (111).

Graw et al (112) selected donors who were HL-A compatible and showed minimal stimulation on mixed lymphocyte culture. The leukemic patients were treated with either 45 mg/kg cyclophosphamide for four days (six patients) or 1,000 rads total body irradiation (two patients) prior to transplantation. Seven of the eight patients had a successful take of the bone marrow graft. Three patients had a severe graft-versus-host reaction and died between 33 and 131 days post-transplant. Two patients had a relapse of leukemia and died within 92 days of transplant, but one patient whose leukemia relapsed lived for 332 days after grafting. The seventh patient was still alive at 451 days with neither GVH disease nor relapse of leukemia (113). Santos et al (114) similarly treated seven patients with leukemia and one with Hodgkin's disease by conditioning with 50–60 mg/kg of cyclophosphamide followed by infusion of HL-A compatible marrow. Marrow engraftment was successful in seven of the eight patients, but six patients survived less than 75 days. One patient succumbed to sepsis at 215 days and the other was living at 77 days at the time of publication. Hong and Bach (115) reported five patients with leukemia who died following HL-A-matched bone marrow transplantation, all of whom had developed severe GVH disease. They concluded that there was an excessive tendency to develop GVH in patients with leukemia compared to those with immune deficiency disease, but this point has been disputed (113).

Other attempts at adoptive immunotherapy have been made by infusing peripheral blood leukocytes rather than bone marrow. Schwarzenberg et al (116, 117) infused between 1 × 10^{10} and 1.2 × 10^{12} peripheral blood leukocytes from patients with chronic granulocytic leukemia into 52 patients with various malignancies, all of whom had neutropenia complicated by infection. In 50 percent of the patients a transient graft was established as evidenced by cytogenetic studies of circulating granulocytes. Twenty-four of the recipients had acute leukemia and in nine of these patients a remission of the leukemia was obtained, six complete remissions and three incomplete remissions. Eight of these nine remissions occurred in patients who were either resistant to therapy or could not be treated due to severe agranulocytosis. In six of the patients who achieved remission status a GVH syndrome was simultaneously present, reinforcing the authors' view that the remissions were of immunologic etiology. No apparent anticancer effect was noted in the patients with nonleukemic malignancies.

Andrews et al (118) injected irradiated tumor cells into healthy volunteers and subsequently transfused thoracic duct lymphocytes from the volunteer into the patient. One child with acute leukemia achieved a complete remission for 15 weeks, but one adult with melanoma died of what appeared to be a graft-versus-host reaction. A third attempt was technically unsuccessful and there was no effect in the fourth case in which lymphocytes from a nonimmunized donor were used.

Although considerable interest has been focused on techniques of adoptive immunotherapy, results continue to be generally disappointing. The occurrence of isolated remissions following bone marrow transplantation from HL-A matched siblings is an encouraging recent development.

VI. Passive Immunotherapy

Attempts at passive immunotherapy, using an antiserum against cancer, date back to the beginning of the century (59, 119). In recent years experimental evidence has accumulated implicating cell mediated immunity as the dominant mechanism in tumor rejection (3) so that enthusiasm has waned somewhat in the use of antibody therapy. There is some evidence to suggest (120, 121) that antibodies may in fact block cell mediated immunity and thus enhance tumor growth, a factor that must be considered in embarking on a course of serotherapy.

Both humans and animals have been used as sources of antibody. Investigators have injected tumor material into animals or human volunteers and harvested subsequently formed antibodies, or have plasmapheresed patients who have shown the ability to suppress growth of their own tumors.

Lindstrom (122) developed hyperimmune sera in rabbits by injection of peripheral leukocytes from patients with myelogenous leukemia. He used the antisera in combination with X-ray therapy in 11 patients with acute leukemia, four of whom achieved complete remissions lasting several months. Four cases, however, were aggravated by serotherapy. Using a similar antiserum Hueper and Russel (123) produced neither remission of leukemia nor diminution of peripheral cell count. DeCarvalho (124) immunized horses with the supernatant of pooled leukemia or tumor cells that had been treated with an antinormal cell serum to precipitate nonmalignant antigens. In 15 patients with leukemia, two patients achieved remissions lasting over two years with others lasting only three months.

Sekla et al (125) produced antibodies specific for leukemia or osteosarcoma in sheep and pigs. The antibodies were obtained by injecting animals at birth with normal human blood cells in an attempt to induce tolerance to normal antigens, and then immunizing the same animals as adults with tumor cells. The 5 patients treated had frequent hypersensitivity reactions to the foreign protein injections but no clear benefit was obtained. Tsirimbas et al (126) gave horse antilymphocyte serum intravenously to six patients with chronic lymphatic leukemia for 12 to 18 days. A transient decrease in the lymphocyte count to 41.5 percent of initial value occurred in three cases.

Several authors have treated tumor patients with antisera obtained in humans. Brittingham and Chaplin (127) gave a patient a transfusion of chronic myelogenous leukemia blood. Several years later, antiserum from this patient was given to the patient with CML, but no benefit was observed. Izawa et al (128) and Sakurai (129) immunized normal volunteers with peripheral blood or bone marrow from patients with acute stem cell leukemia or chronic mylogenous leukemia. Leukoagglutinin titres were demonstrated in the volunteers. Infusion of the antiserum into the patients with leukemia caused a decrease in the percentage of blast cells as well as a decrease in the total leukocyte count lasting less than 24 hours. Laszlo et al (130) injected normal lymphocytes into volunteers and used the resulting antilymphocyte serum to treat three patients with refractory chronic lymphocytic leukemia. Each infusion caused a significant drop in the lymphocyte count and decreased lymph node diameters. A prompt fall in the lymphocyte count was always observed within 48 hours but the duration of response varied, the longest being several weeks. No change in the differential white count was observed. Skurkovich et al (131) submitted 18 children with acute leukemia in remission to plasmapheresis and leukopheresis. Ten of these children were treated with repeated infusions of autologous plasma and autologous leukocytes in an attempt to sustain the state of antileukemic immunity that could be present in early remission. When compared to a control group, there was a statistically significant increase in the duration of remission in the treated group, from 173 days to 491 days. Patients who had achieved only partial remission did not respond to this form of therapy.

VII. Conclusions

The rational immunotherapy of human leukemia requires that tumor antigens can be shown to differ from normal antigens and that a host response can be mounted against the abnormal antigen. Although there is some evidence for the existence of leukemia-associated antigens, further identification and isolation of these antigens are necessary for more specific therapy to proceed.

The large number of clinical trials of immunotherapy conducted in the past ten years have contributed some further data on the nature of the host response to immunological procedures, but there has been little success in causing regression of disease. Limited success has been claimed in prolongation of remission in childhood leukemia using active immunotherapy, but these studies have generally suffered from lack of controls. Considerable interest has been focused on bone marrow transplantation techniques, but results continue to be disappointing. There are many single cases apparently responding to immunotherapeutic procedures that may be regarded as very interesting although far from conclusive.

At the present time, it appears that immunotherapy of human leukemia and other malignancies remains a promising field, as it has been since the nineteenth century, and that further investigations are warranted. Success with animal models in isolation of tumor antigens, documentation of host response, and cure or prevention of malignant disease continues to give impetus to this field.

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Spontaneous Rupture of an Abdominal Aortic Aneurysm into the Inferior Vena Cava: A Case Report and Review of the Literature

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Abstract

Spontaneous rupture of an aortic aneurysm into the inferior vena cava with fistula formation is rare. Only 42 cases were found on review of the literature.

The patients clinically present with abdominal pain, pulsatile mass, and continuous bruit. Because of rise in venous pressure edema of the lower extremities appears. In most of the reported cases the aneurysm was due to arteriosclerosis. A case of a 74-year-old patient admitted with lower back pain of two weeks' duration is reported. A pulsatile mass was found in the umbilical area with a continuous bruit. The patient expired the day after admission and at autopsy an arteriosclerotic aneurysm perforating into the inferior vena cava was found.

Introduction

Spontaneous rupture of an aortic aneurysm into the inferior vena cava is rare. A careful bibliographic search disclosed only 42 cases since the first description of this condition by Syme in 1831 (1).

The purpose of this report is to present a case of aortocaval fistula and to give a brief review of the pertinent literature.

Case Report

A 74-year-old white man entered Hines Veterans Administration Hospital because of severe lower back pain of two weeks' duration. The patient was in moderate respiratory distress, and scattered lung rales were audible. The heart showed moderate enlargement and was in atrial fibrillation. These were no murmurs. Abdomen was soft, and nontender; no masses were felt. The other physical findings were unremarkable. The temperature was 99.6°F., the pulse 88, the blood pressure was 168 systolic, 120 diastolic; blood pressure in the lower extremities was not taken. Hemoglobin was 14.9 grams percent, the hematocrit 44.4 percent, and the white blood cell count 13,700. The total bilirubin was 2.6 milligrams percent, the alkaline phosphatase was 125 units. The sodium was 142 milliequivalents, the potassium 4.5 milliequivalents, the chlorides 101 milliequivalents, and the carbon dioxide 22 milliequivalents per liter; the urea nitrogen was 27 milligrams per 100 milliliters. Blood and urine cultures were negative. A Venereal Disease Research Laboratory test was nonreactive. An electro-cardiogram revealed atrial fibrillation with old inferior myocardial infarction. X-ray study of the chest showed cardiomegaly and pulmonary congestion. No flat plate of the abdomen was taken.

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Hospital Course

A few hours after admission the patient developed mild fever, chills, and abdominal pain radiating toward the right hip. The following day he had a tachycardia of 120/min and his blood pressure dropped to 90 systolic, 60 diastolic. A pulsatile mass in the umbilical area was palpated and a continuous bruit was heard. Very quickly after the onset of shock, a cardiac arrest occurred and resuscitation attempts were unsuccessful.

At autopsy a large arteriosclerotic aneurysm involving the abdominal aorta was found (Fig. 1). It measured 15 × 7 × 5 centimeters and extended distally to involve both iliac arteries. On dissection of the inferior vena cava a connection between the aneurysm and the lumen of the inferior vena cava was demonstrated with the area of perforation located on the posterior surface of the aneurysm, 10 cm below the origin of the renal arteries. No blood was present in the peritoneal cavity or retroperitoneal space and the aneurysm was filled with partially organized blood clots.

The connection between the aneurysm and the inferior vena cava had ragged edges (Fig. 2). The opening measured approximately 1.4 cm in diameter.

Histologically the aneurysm was arteriosclerotic in nature and no granulomas or inflammatory infiltrates in the wall of the inferior vena cava were noted.

Review of the Literature

From the world literature we collected 42 cases of spontaneous aortocaval fistula due to rupture of an aortic aneurysm into the inferior vena cava. The age of all cases, including our own, ranged from 21 to 78 years, and its distribution is shown in Table I. The incidence was highest in the sixth decade. All but two of the 42 patients were males. Arteriosclerosis represents the predominant etiologic factor. In two patients the aneurysm was associated with syphilis (2,

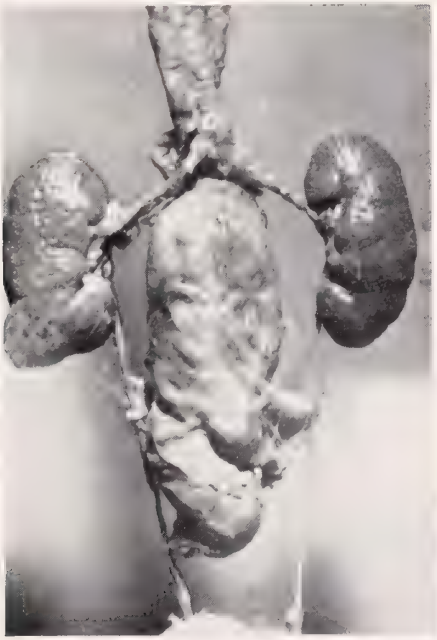

FIG. 1. The photograph shows large aneurysm of the lower abdominal aorta with bulbous extension into the iliac arteries.

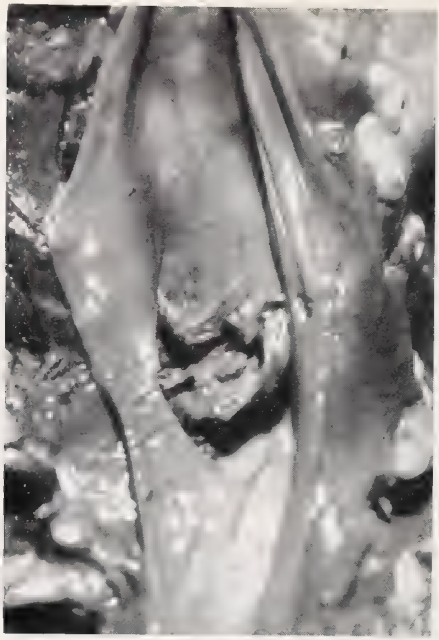

FIG. 2. Close-up of ragged perforated border of inferior vena cava with blood clots.

TABLE I

Age Distribution among 37 Patients

Years	Number of cases
20–29	2
30–39	1
40–49	2
50–59	8
60–69	17
70–79	7

3), and in one, with Marfan's (4) syndrome. The rupture usually occurs in the right postero-lateral wall and the fistula is located above the inferior vena cava bifurcation, its size ranging from 1.2 to 4 centimeters in diameter.

Signs and Symptoms

A. Pain appears as the main presenting symptom (see Table II). Variously described by the patients as mild, sometimes unrelenting, or violent, and excruciating, it is usually localized in the lower back, the abdomen, or both, and may radiate toward the groin, the thighs, and the lower legs. The wide variability of the pain pattern, especially as an isolated symptom, may lead to confusion with pancreatitis, perforated ulcer, cholecystitis, peritonitis, lumbar arthritis, herniated nucleus pulposus, or myocardial infarct (5).

TABLE II

Symptoms and Signs in 37 Cases of Aortocaval Fistula due to Rupture of Aortic Aneurysm into the Inferior Vena Cava

Local	
Pain	
abdominal	9
back	10
abdominal and back	4
radiating to legs	4
Pulsatile abdominal mass	30
Bruit	
continuous	25
systolic	3
Thrill	13
Systemic arterial insufficiency	
CNS (syncope, confusion, coma)	6
Shock	9
Renal	4
oliguria, anuria	4
azotemia	15
Venous hypertension	
Edema	12
Hepatomegaly	9
Ascites	3
vomiting	8
Hematuria	
macroscopic	3
microscopic	4
rectal bleeding	2
Pulsatile veins	3

According to Mannick (5, 6), the sudden onset of abdominal or back pain in a patient known to have an aneurysm of the aorta strongly suggests an aneurysmal rupture.

B. A pulsating mass is usually palpable in the mid-abdomen; it rarely protrudes into the left or right quadrant or into the hypogastric area. The configuration of the mass varies from round to elongated, with ill-defined margins and the sizes range from 6 to 8 centimeters, up to 12 to 15 centimeters.

Hufnagel (7) described a patient with two abdominal masses; one soft, and ballotable in the right upper quadrant, the other hard and pulsatile to the left of the midline. Upon surgery, the former was identified with the inferior vena cava, the latter with the aneurysmal sac.

In a few patients palpation of the mass may evoke or exacerbate the pain.

The diagnosis of aneurysm preceded the rupture by varying intervals: five years (8), two years (9), one year (10), several months, or only weeks (11). In a few instances the fistula developed following hospitalization (12, 13).

C. A bruit represents the third major diagnostic clue. It usually is loud, harsh, continuous with a systolic accentuation. Seldom it is systolic only. While most noticeable over the mass, the bruit can also be detected over the entire abdomen, the lumbo-sacral area, and sometimes even over the tibia (7). In about one-fourth of the cases a thrill is palpable.

Strong pressure over the site of the fistula may temporarily abolish the murmur (14), but this diagnostic maneuver was generally not performed.

Because of the atheromatous wall, the fistula enlarges with time and the increasing hemodynamic overload produces other symptoms and signs. As the venous pressure rises, edema may appear in the lower extremities and sometimes may involve progressively the genital area, lower abdomen and trunk. It is of a pitting type, and is unresponsive to digitalis or diuretics.

In two cases edema was the only presenting symptom (15, 16).

According to some reports, the peripheral veins may become dilated and tortuous, and sometimes pulsatile (15, 17); in other cases, the superficial abdominal and jugular veins are engorged.

Hepatomegaly of varying extent has been observed, occasionally associated with ascites (8, 15).

Some patients may initially complain of vomiting (14, 18, 19), which is probably due to severe congestion of the liver and gastric mucosa as the fistula develops (19). The increased pressure in the pelvic veins may produce a misleading profuse rectal bleeding (13), while the lowered mean aortic pressure may cause central nervous system symptoms varying from syncope (20–22) and mental confusion (11) to lethargy (14, 23) and coma.

Decreased arterial flow and venous stasis distal to the fistula sometimes cause cyanosis of the lower part of the body, in contrast to the pallor above the umbilicus (22). The femoral pulses may weaken and the radial pulse may become bounding.

Some reports describe renal symptoms such as oliguria, anuria and uremia (3), which are probably due to decreased arterial perfusion and venous engorgement in the kidneys.

Azotemia was present in 15 of the reported cases, gross hematuria was found in three patients (20, 22, 24) caused by hypertension in the hypogastric veins with hemorrhage into the bladder mucosa (24).

Four other patients had microscopic hematuria (11, 25, 26).

Diagnostic Procedures

An electrocardiogram is of a minor importance, except for eliminating the possibility of other cardiovascular complications.

Chest x-ray shows cardiomegaly in one-third of the cases, with pulmonary congestion in some.

Abdominal radiograms, which should always be performed in an elderly man with back pain, may reveal findings suggesting an abdominal aneurysm such as a paravertebral soft tissue mass, often outlined by a calcified rim, and displacement of the neighboring structures. In addition, one may see indistinct margins of the mass which extend beyond the calcified rim and obliterated psoas shadows. An aortogram was of diagnostic value in four patients, but need not be routinely performed if the diagnosis can be established without its aid.

Hemodynamic studies show that the venous oxygen saturation is high following establishment of arterio-venous communication, especially at the level of the fistula (8), and the blood volume, cardiac output and central venous pressure are increased, all of which revert to normal after surgery.

Surgery

Of 35 patients who have undergone surgery, 17 (48.5%) survived. The procedure of choice consists of resection of the aneurysm with homograft replacement, and repair of the fistula in the inferior vena cava.

Cardiac arrest (4, 18, 21, 28) and pulmonary embolism (7, 24) figure among the most frequent causes of death during or immediately after the surgery. An aortoduodenal fistual developed in three patients (3, 15, 17), within six months.

Conclusions

1. Arteriosclerosis represents the most common etiologic factor in spontaneous rupture of an abdominal aneurysm into the inferior vena cava.
2. Pain, a pulsatile abdominal mass, and a continuous bruit form the diagnostic triad. On the other hand, the presence of central nervous system symptoms, hematuria, vomiting or rectal bleeding may mislead the diagnostician.
3. Abdominal x-ray and aortogram often aid in arriving at the correct diagnosis. A flat film of the abdomen should be done in every instance of unexplained back pain in an elderly man.
4. Prompt surgery is essential to save the patient's life.

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Obstructive Jaundice and Portal Vein Obstruction—Rare Complications of Peptic Ulcer

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Among the causes of jaundice due to obstruction of the extrahepatic biliary tree, common bile duct stone is the most frequent, followed by neoplasm of the pancreas and ampullary region. Inflammatory processes, intrinsic or extrinsic to the extrahepatic bile ducts, are a less frequent cause of obstructive jaundice, and, in this group of diseases, peptic ulcer is the rarest (1–5).

As radiologic studies are frequently performed to elucidate the etiology of obstructive jaundice, the radiologist should remember that benign duodenal ulcer may be associated with obstruction of the bile ducts and that early diagnosis is crucial in the management of these cases. Reports have been published which demonstrate the possible lethal nature of this nonmalignant disease if it proceeds uncorrected (6). Not infrequently the differential diagnosis between a neoplasm and the inflammatory mass associated with peptic ulceration may not be possible even at exploratory laparotomy. One additional complication of duodenal ulceration, which is even rarer than obstructive jaundice, is obstruction of the portal vein as the result of thrombosis or occlusion due to adhesions or inflammatory mass, leading to portal hypertension and its serious sequelae (7, 8).

The present report includes three cases of obstructive jaundice secondary to peptic ulceration, and a fourth in which jaundice seemed imminent as demonstrated by the increasing size of the gall bladder on repeated oral cholecystography. In one of the four cases, portal vein obstruction developed late in the course of the disease and the patient died as the result of massive upper gastrointestinal bleeding from esophageal varices.

Case Reports

Case 1, B.S. A 63-year-old white women noted weakness, anorexia, and a five-pound weight loss during the four months prior to admission. Scleral and skin icterus and light-colored stools were present for four days. In addition, the patient complained of gaseous distention and slight epigastric distress. A peptic ulcer had been demonstrated on gastrointestinal series at another hospital three years prior to the present admission. A history of transfusion, thorazine ingestion, or hepatitis contact was not obtainable. The physical examination was normal except for the presence of jaundice. The gall bladder and liver were not palpable. The urine contained bile. The initial serum bilirubin was 7.6 mg per 100 ml with a direct reacting bilirubin of 6.8 mg; this rose to 12.2 mg% in three days. Similarly, the alkaline phosphatase of 7.9 KA units on admission increased to 20 KA units. All other laboratory studies were within normal limits. Roentgen examination of the gastrointestinal tract showed a deformed duodenal bulb with an ulcer crater. The ulcer extended to the pyloric channel. There was evidence of a noninfiltrating periduodenal mass (Figs. 1 a & b). Surgical exploration eight days later revealed the gall bladder to be dilated and under tension. A mass in the region of the first and second portions of the duodenum

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extended up to and involved the common bile duct. During retraction, one of the retractors inadvertently opened the duodenum and upon viewing the mucosa an ulcer with an indurated margin was visualized. In the belief that it represented a neoplasm, a palliative gastroduodenectomy with an antecolic gastroenterostomy was performed. The common hepatic duct was transected just above the level of the cystic duct and anastomosed to the duodenum. The resected specimen showed a large punched-out ulcer at the pylorus with

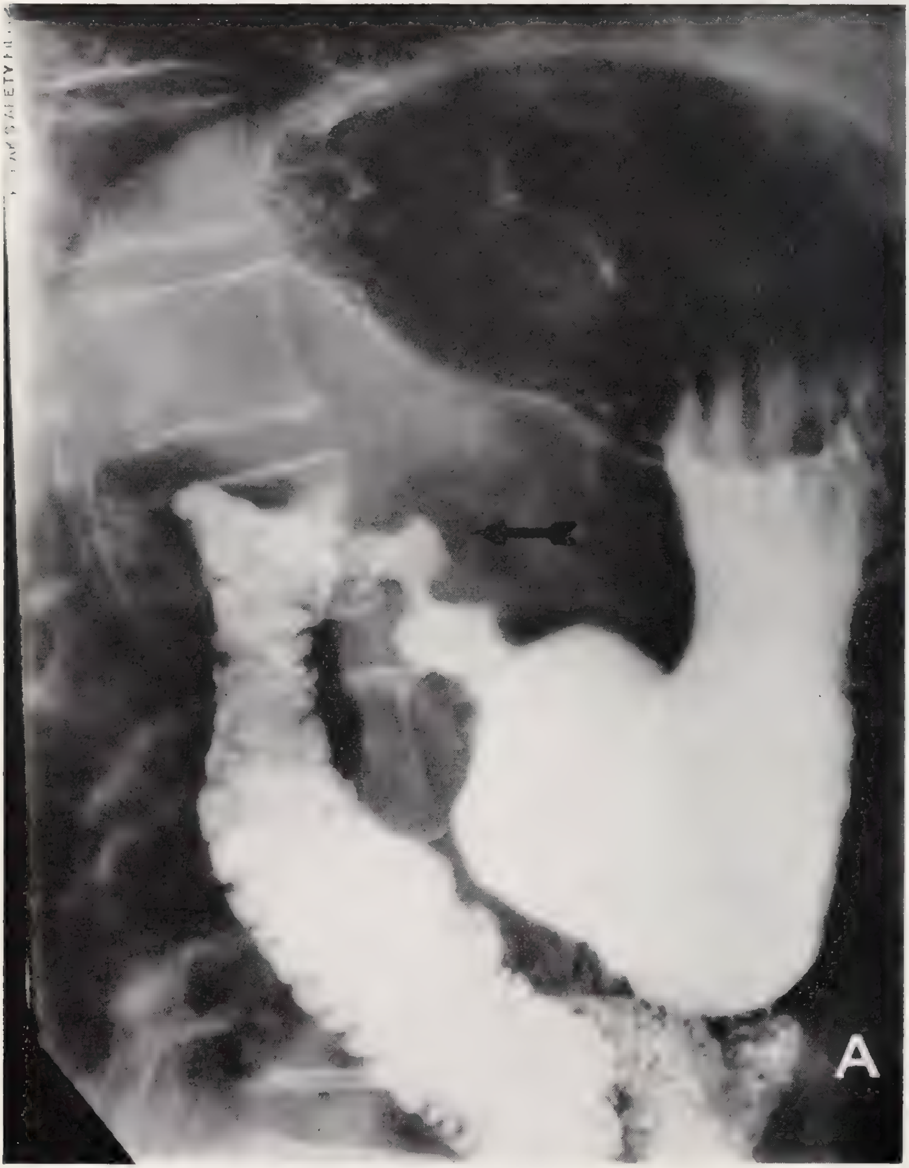

Fig. 1a. The duodenal bulb is markedly deformed with an ulcer crater at the base (arrow). The surrounding mucosa in unsharp due to edema. Well-defined delimitation distally and irregular appearance of pyloric antrum create an impression of a mass. The duodenal loop is normal. Linear barium streak at the lower margin of the ulcer is in contracted inferior fornix of the bulb.

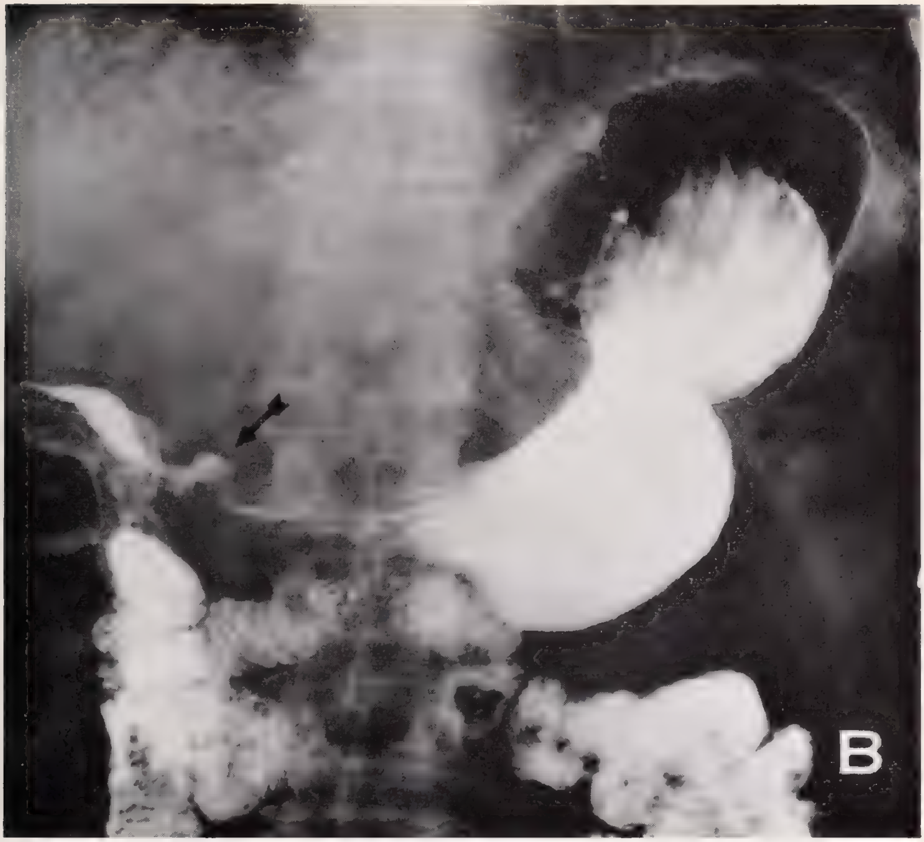

Fig. 1b. Frontal projection demonstrates the duodenal ulcer (arrow) which is discrete and well defined with no marginal nodulations. The antral mucosa is normal. The distal end of the inflammatory mass displaces to apex of the bulb laterally and caudally.

slightly rounded margins measuring 14 mm in its greatest diameter. The surrounding mucosa was considerably reddened and edematous. Histologically this was a chronic peptic ulcer with no evidence of tumor.

The serum bilirubin returned to normal about three weeks after surgery. The patient was discharged six weeks after admission free of jaundice and epigastric distress.

Comment

The cause of obstructive jaundice was the direct involvement of the common bile duct in an inflammatory mass consisting of adhesions, granulation tissue and edema due to calloused duodenal ulceration. This inflammatory mass resulted in deformity of the duodenum, common bile duct and hepato-duodenal ligament and this, in association with the presence of a mass made it impossible to differentiate this process from malignant disease, even at surgery. Roentgen diagnosis, however, was that of ulcer with a noninfiltrative mass. With a previous history of peptic ulceration and awareness of the possible connection between ulcer disease and jaundice, the correct diagnosis could have been made.

Case 2, H.H. A 69-year-old man was first admitted to the hospital with a two-week history of epigastric pain, anorexia and increasing jaundice. The patient gave a long history of ulcer with two previous bleeding episodes. The patient felt that the character of the present pain

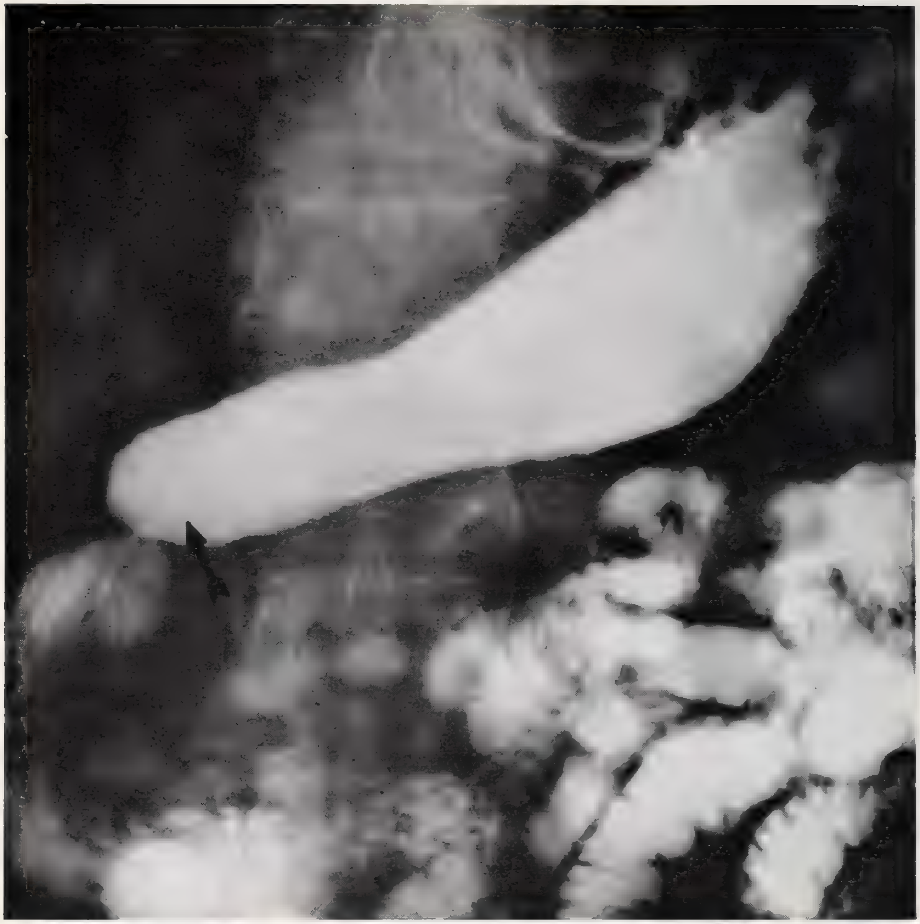

Fig. 2. The duodenal bulb is contracted and rotated posteriorly. The ulcer crater is seen through the antrum of the stomach which lies more laterally than usual. Similar displacement is not infrequent following gallbladder surgery, with adhesions development between the antrum, duodenal bulb and gallbladder bed. The ulcer crater is discrete and is not surrounded by an identifiable mass.

was identical with the previous ulcer pain. Physical examination was unremarkable except for jaundice. Pertinent laboratory findings were a total serum bilirubin of 6.3 mg% and alkaline phosphatase of 51 KA units. The cephalin flocculation was normal. Bile was present in the urine. A gastrointestinal series showed a small duodenal bulb with an ulcer crater (Fig. 2). The patient was placed on an ulcer regimen. An intravenous cholangiogram prior to admission had failed to visualize the biliary system. However, a repeat cholangiogram after the relief of jaundice on an ulcer regimen showed a normal gallbladder and common bile duct without biliary calculi. The hepatic radicles appeared slightly wide. Eighteen months later, the patient was readmitted for epigastric pain and gastrointestinal bleeding. The physical examination was unremarkable except for slightly elevated blood pressure and 4+ positive guaiac stools. A subtotal gastrectomy was performed. The resected specimen demonstrated a duodenal ulcer. The liver, gallbladder and bile ducts were normal.

Comment

In this patient a correct diagnosis was made and medical therapy for reactivation of peptic ulcer of long duration was instituted with relief of jaundice. It is almost certain that the peptic ulcer was the cause of obstructive jaundice. There was no history of hepatotoxic drug ingestion or transfusion. There were no biliary calculi present on cholangiography and at surgery. Only the bile ducts (on cholangiography) proximal to the site of duodenal ulceration were dilated.

Case 3, S.H. This is a 68-year-old white man who first entered the hospital two years previously for a bleeding ulcer. A gastrointestinal series at that time revealed duodenal deformity. A second admission two months later was for obstructive jaundice. At surgical exploration, the right lobe of the liver was small and was associated with hypertrophy of the left lobe. The gall bladder could not be found because of marked duodenal deformity associated with an inflammatory mass, the duodenum being pulled up to the porta hepatis. The common bile duct was normal. The mesenteric and omental veins were greatly dilated and in conjunction with splenomegaly suggested portal hypertension. A biopsy of the liver revealed intrahepatic cholestasis. There was no cirrhosis. The third admission six months later was for recurrence of jaundice, eructations, and a distended abdomen. Physical examination revealed ascites and splenic enlargement. Laboratory examination revealed a normal BUN, total protein of 7.5 mg, per 100 ml with an albumin of 2.9 g and globulin of 4.6 g, SGOT of 147 units per ml; bilirubin of 27.2 mg; per 100 ml, alkaline phosphatase of 8.1 KA units, and a cephalin flocculation of 1+. A gastrointestinal series revealed a hiatus hernia, and a duodenal ulcer associated with an inflammatory mass (Figs. 3a & b). The jaundice decreased on an ulcer regimen and antibiotics. A splenorenal shunt was subsequently performed. At operation, a firm mass involving the hepatic pedicle was found. The portal vein pressure measured 350 mm of H_2O. He was readmitted four months later with hematemesis. This led to hepatic coma but the patient recovered with routine measures. On this admission, esophageal varices could not be demonstrated. Surgery was considered but deferred because of the general condition of the patient. His final admission two years after the initial admission was for increasing jaundice and pruritis. Physical examination revealed a liver enlarged two fingers below the right costal margin. It was smooth and slightly tender. The stool was persistently positive for blood. The serum bilirubin was 23.3 mg. The alkaline phosphatase ranged between 7 and 11 KA units, and the cephalin flocculation was 2+. A gastrointestinal series again showed the duodenal ulcer, albeit smaller, with a large inflammatory mass. He was treated with an ulcer regimen and oral neomycin but could not tolerate the high protein in a Sippy diet. Gastric suction produced coffee-ground material which was strongly positive for blood. He progressively went into hepatic failure and died of hepatic insufficiency and continued gastrointestinal bleeding. At autopsy the abdominal cavity contained 1500 cc of clear yellow fluid. The first portion of the duodenum was firmly adherent to all structures in the region of the porta hepatis. An end-to-side anastomosis between the splenic and left renal vein was patent. The liver weighed 1750 gms. Its surface was smooth, except for slight granularity on the surface of the left lobe of the liver. The portal vein was dilated, measuring 3.5 cm in circumference at its origin but became stenotic at its entrance into the liver substance due to surrounding dense fibrosis. At this point, one branch of the portal vein was completely occluded. The common hepatic duct and the common bile duct were normal. The gallbladder was shrunken. At its entrance into the liver substance, the common hepatic duct appeared narrowed by surrounding dense fibrosis. Just beyond this area of narrowing, the intrahepatic biliary radicles were markedly dilated. The pancreas appeared normal. The esophagus showed varices. Some of these appeared thrombosed and there was an erosion over a dilated vein in the cardia of the stomach. In the first portion of the duodenum a 1.1 × 0.4 cm ulcer crater with rounded edges was seen. The duodenum in this area was firmly adherent by dense fibrous adhesions to the liver in the region of the porta hepatis.

The final diagnosis was chronic peptic ulcer of the duodenum penetrating and causing

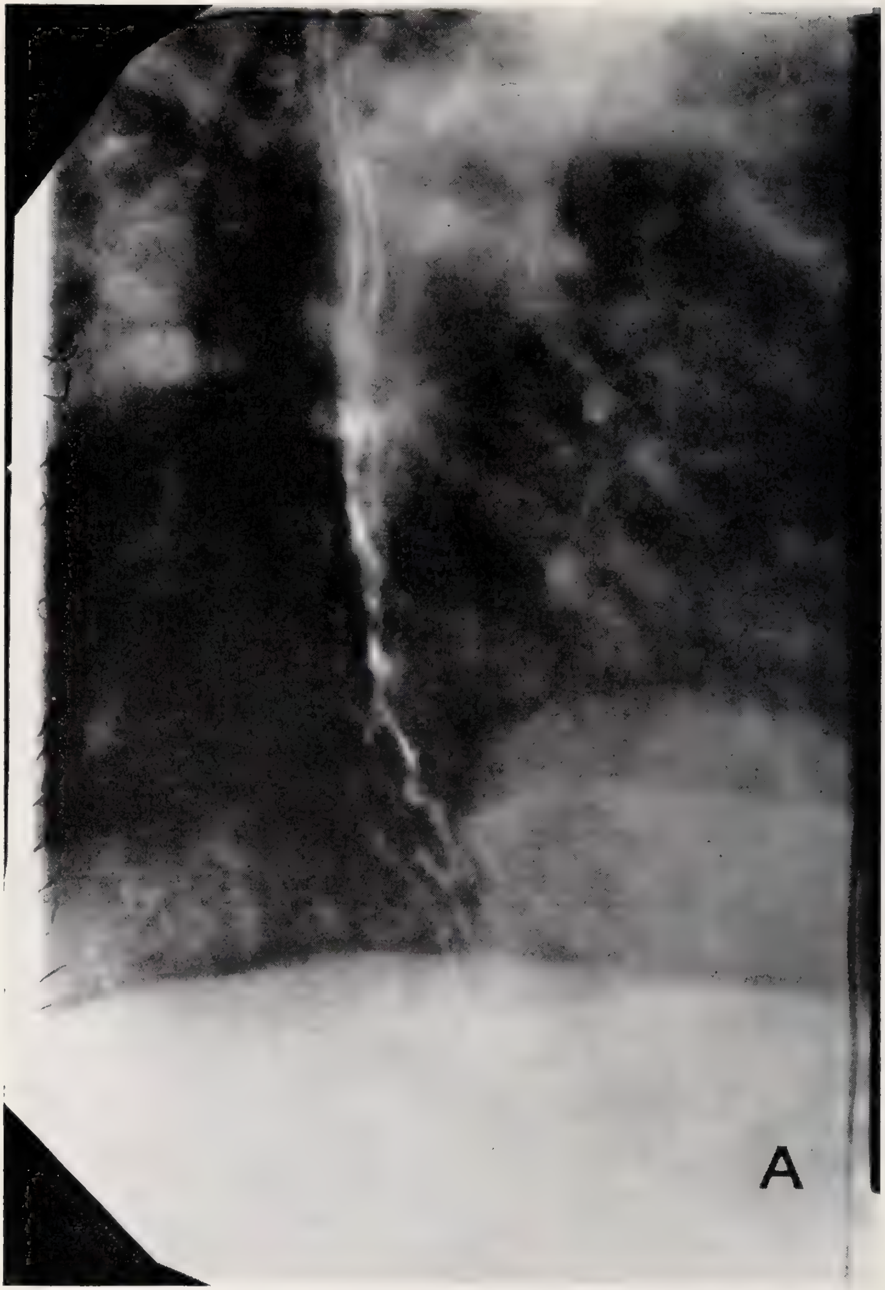

FIG. 3a–b. Mucosal study of the esophagus shows typical appearance of varices. (b) A smooth discrete ulcer crater lies in the center of a mass deforming and narrowing the entire duodenal bulb. The distal margin of the mass is fairly well defined and the folds at the junctional zone are thick but not nodular. The base of the bulb had a triangular configuration. The mucosa is not nodular but effaced due to edema. The antrum of the stomach and the duodenal loop are normal. The central location of ulcer with equal narrowing (due to spasm and edema) distally and proximally produces the so-called "bow-tie" deformity of peptic ulcer.

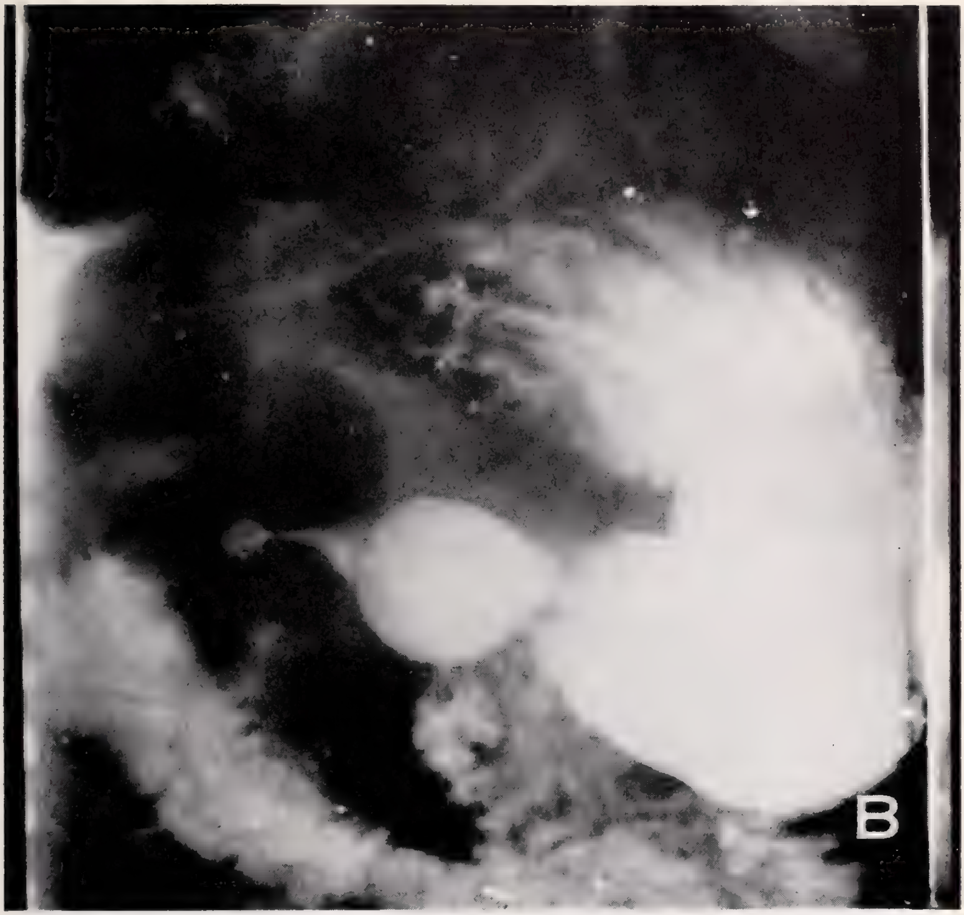

Fig. 3b.

stenosis of the common hepatic duct which led to biliary cirrhosis and obstruction of the portal vein causing ascites, esophageal varices and multiple gastric erosions.

Comment

This patient with a long history of ulcer was admitted with gastrointestinal bleeding, followed closely by the development of obstructive jaundice. At surgery a large adherent mass was found at the porta hepatis. The common bile duct was normal. There was evidence of portal hypertension. In the belief that the mass was a neoplasm only liver biopsy was performed. His subsequent admissions were due to progressive extrahepatic biliary obstruction and portal vein obstruction which led to death due to hemorrhage from varices and gastric erosions. Because of the irreversible deformity and obstruction of the bile ducts and portal vein due to adhesions and kinking, the course of the patient was progressively downhill. Definitive surgery for ulcer became unfeasible after initial exploration because of progressive and more serious portal vein obstruction and also because carcinoma could not be excluded. In this case, biliary cirrhosis might have coexisted with peptic ulcer. This, however, is unlikely because of the normal liver biopsy at first exploration and also because of the presence of dilated intrahepatic biliary radicles.

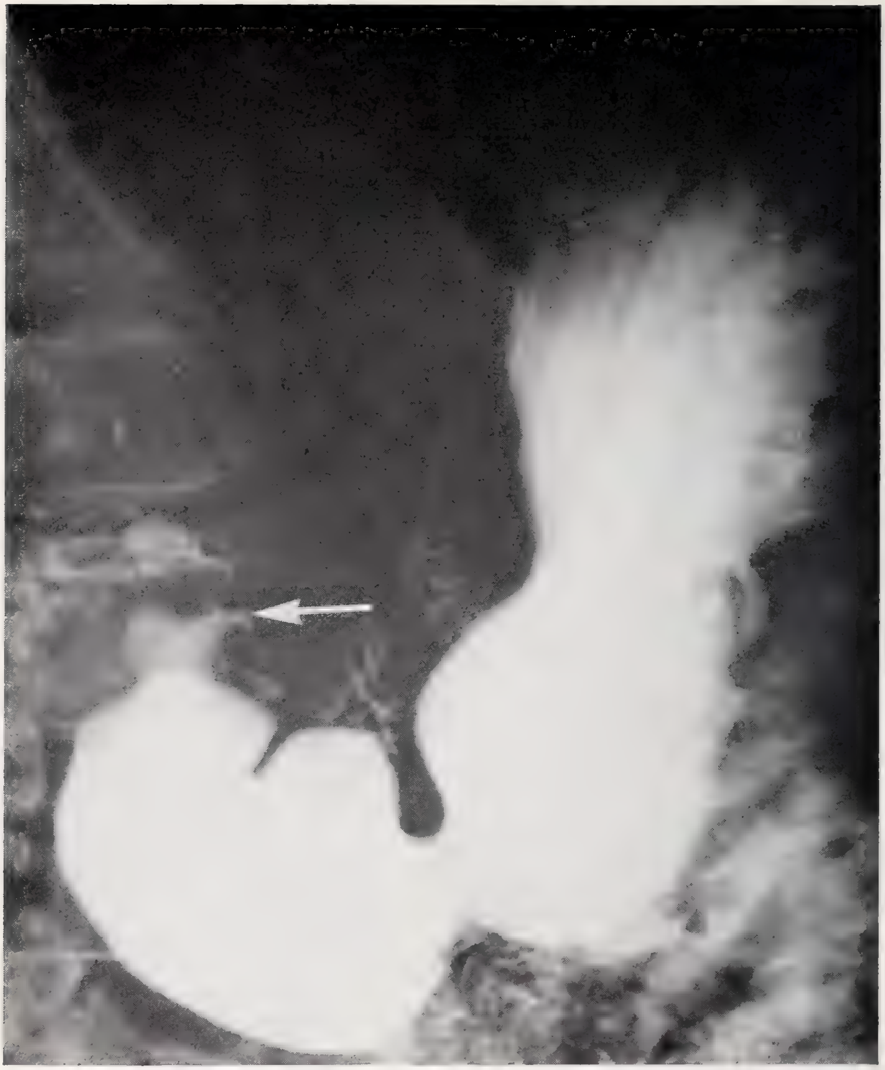

FIG. 4a–d. A discrete ulcer crater (arrow) is present near the superior fornix of the duodenal bulb with thick and edematous mucosal folds radiating to its margin. The post-apical segment of the intraperitoneal first part of the duodenum is stretched due to fixation. There is no evidence of tumor nodules or duodenal loop abnormality. (b) Frontal view reveals posterior rotation of the bulb. The antral narrowing is due to antral systole. (c) Oral cholecystography shows normal gallbladder without calculi. (d) A few months later the gallbladder, well-opacified, is considerably larger and the ducts visualized are at the uppermost limit of normal in caliber.

Case 4. A 65-year-old man with a history of ulcer for five years complained of acute abdominal pain. At the time of acute pain his alkaline phosphatase was 8.1 KA units and the Bilirubin 0.8 mg per 100 ml. The possibility of acute cholecystitis in a patient with peptic ulcer was considered. The patient was treated with antacids with considerable improvement. On an upper gastrointestinal series, an ulcer crater was demonstrated at the base of the duodenal bulb (Figs. 4 a and b). The stomach was large with a considerable amount of

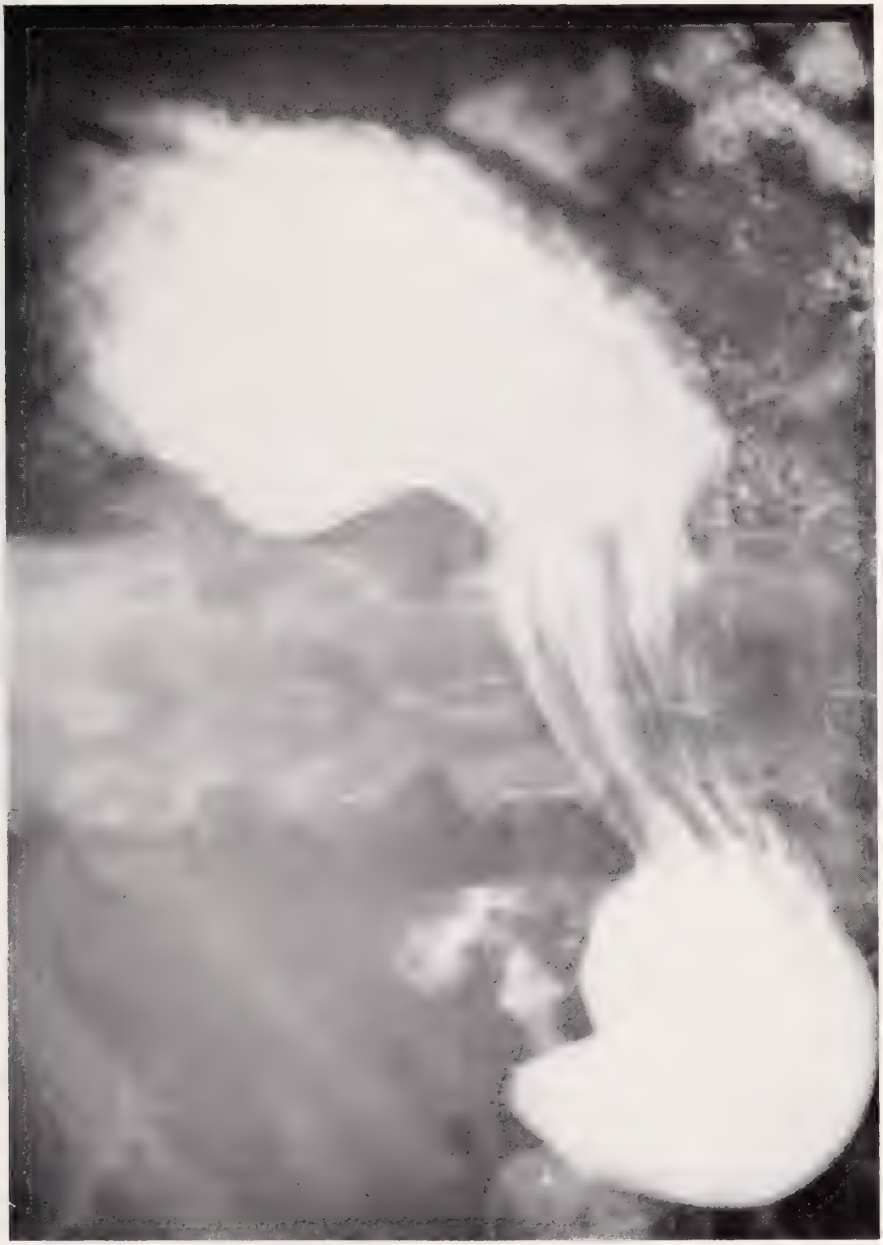

Fig. 4b.

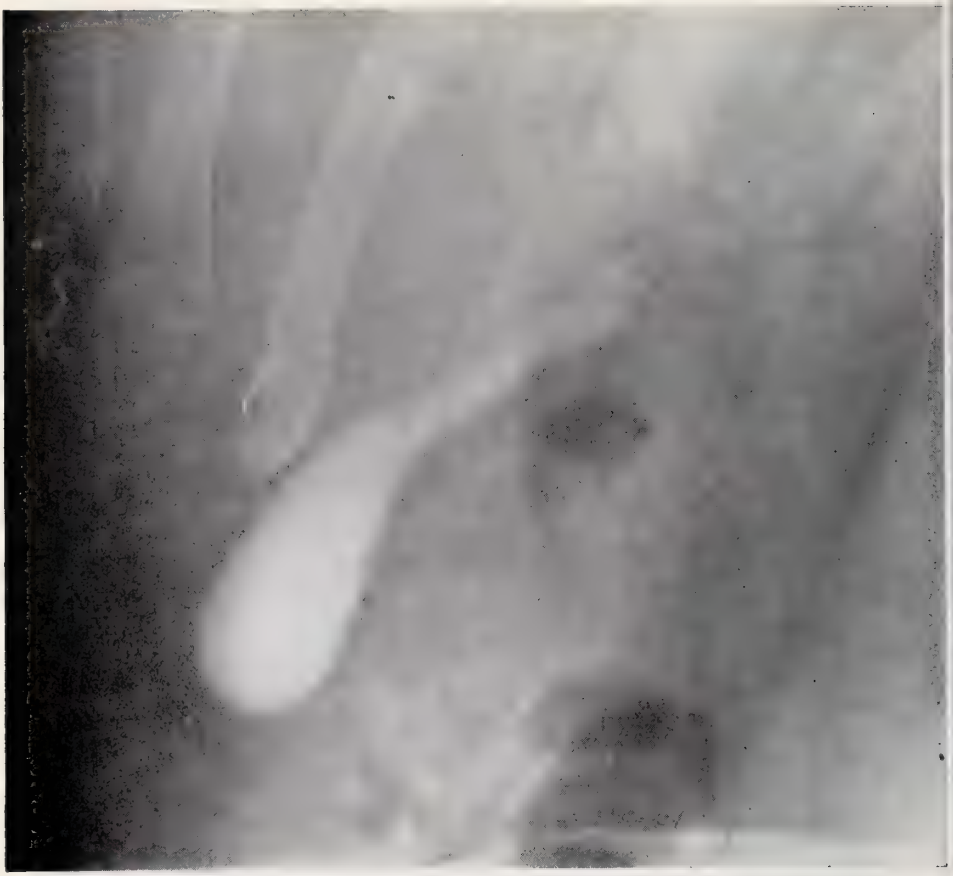

FIG. 4c.

secretions. Oral cholecystogram showed a well-opacified, normal-sized gall bladder without calculi (Fig. 4 c). Next admission two years later was for symptoms of active ulcer and heartburn. Gastrointestinal series again revealed a fairly large active duodenal ulcer. Hemoglobin, bilirubin, and alkaline phosphatase were normal. On oral cholecystogram, the gallbladder was found to be considerably larger than two years earlier. Treatment was directed primarily at the ulcer. The patient improved and was discharged without surgery. Readmission six months later was again for acute abdominal symptoms and tarry stools. Surgery was recommended but this was refused. The ulcer crater could again be demonstrated on the gastrointestinal examination. Gallbladder examination showed poor opacification on the second day after 3 grams of Telepaque®. On the third day the gallbladder was considerably larger and enlarged ducts were opacified. Stones were not present (Fig. 4 d). The patient subsequently underwent surgery. A 1-cm ulcer crater was noted just beyond the pyloric channel. There were numerous adhesions between gallbladder, liver, duodenum, and stomach. The stomach appeared dilated and the wall was hypertophied due to mild obstruction. No calculi were seen in the gallbladder or bile ducts. Partial gastrectomy and vagotomy were performed. Histologic examination confirmed the diagnosis of benign ulcer with fibrosis and marked edema around the ulcer.

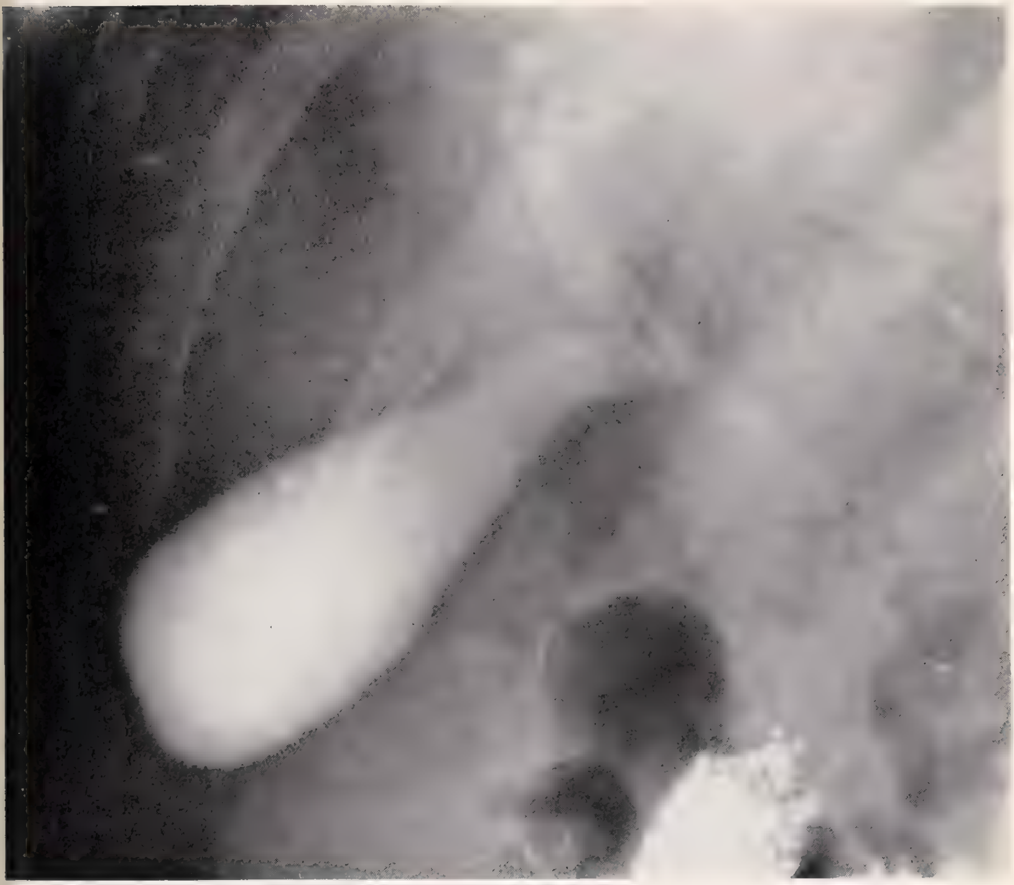

Fig. 4d.

Comment

In this patient, clinical jaundice or hyperbilirubinemia was not demonstrated. However, his initial admission was for acute abdominal pain which clinically suggested acute cholecystitis. This can be explained on the basis of obstruction of the cystic duct due to adhesions, leading to acalculous cholecystitis. A similar symptom complex (due to adhesions and edema of Curling's ulcer) has been reported in patients with burns. The gallbladder initially was normal but later increased in volume. Two possible explanations can be offered. One is that the parasympatholytic drugs, utilized in the treatment of ulcer, were the cause of the gallbladder dilatation. The other explanation is that this enlargement was due to partial obstruction of the common duct which could have been the initial stage of a progressive extrahepatic biliary tract obstruction.

Discussion

Du Pree (9) modified Da Gradi's classification of the possible pathophysiology of jaundice in ulcer disease as follows:

I. Occurrence of two separate conditions such as duodenal ulcer with hepatitis or biliary duct calculi or pancreatic-biliary neoplasm (10);

II. Cholecystitis and choledochitis initiating the ulcer. In this regard Hickenbotham (10) quotes Santos et al. and Bollman et al., as stating that experimental obstruction of the common bile ducts in dogs results in the development of peptic ulcer in a high percentage of cases. Strangely enough, duodenal ulcer due to biliary obstruction has not been reported in man;

III. Munster et al (11) have reported acalculous cholecystitis and even jaundice associated with Curling's ulcer in ten out of 2456 burn patients. He stated that periduodenal inflammatory changes and edema resulting from Curling's culcer cause kinking and obstruction of the cystic duct resulting in acalculous cholecystitis and, occasionally, jaundice due to common bile duct involvement;

IV. Peptic ulcer disease as the causative factor in (A) an unusual case (quoted by DuPree (9)), hemorrhage secondary to peptic ulcer dissected submucosally, abscessed and intussuscepted, producing periportal and pericholedochal edema and jaundice, and in (B) obstruction of the common bile duct by: 1. Perforation into the duct—a rare occurrence, and 2. Periduodenitis, peri-Vaterian, and or pericholedocal inflammation and subsequent fibrosis.

On this subject most of the authors have reported the site of the ulcer to be the descending duodenum near the papilla of Vater with involvement of the adjacent common bile duct. Some cases, however, demonstrated ulcer in the region of the bulb. Very few cases revealed inflammatory mass involving the lesser omentum with obstruction of the common bile duct at the porta hepatis. Cases number 1 and 3 in our series showed peptic ulcer at the pyloro-duodenal region and obstruction of the bile duct at the porta hepatis. In case 3 the inflammatory mass also extended caudad to involve the portal vein.

3. Pancreatitis with or without abscess. DuPree quotes Sanweiss, as stating that, in a series of 270 consecutive perforated ulcers, 50 had pancreatitis.

The usual pathogenesis of obstructive jaundice seems to be periduodenitis with or without perforation leading to adhesions, edema and pancreatitis, and subsequent compression of the bile ducts. Obstruction may occur near the papilla of Vater if the ulcer is located in the descending duodenum or at the level of the porta hepatis if peptic ulceration involves the pyloroduodenal area with shortening of the lesser omentum and fixation of the duodenum in the porta hepatis. The extent and course of the jaundice is dependent on the degree of compression and the nature of the pathological process. If adhesions produce kinking of the bile ducts or portal vein irreversible luminal compromise may ensue with serious sequelae. Perforation into the common bile duct is either acute or a late manifestation. In the latter situation, jaundice is present prior to perforation, and surgery is, therefore, often performed before fistulae are established.

The correct diagnosis involves differentiating inflammatory from neoplastic mass. Neoplasms, which are most often the cause of jaundice, include carcinoma of the pancreas, gallbladder and bile ducts and metastatic carcinoma. Roentgenologically this differentiation may be difficult, especially if roentgen evidence of mucosal infiltration and amputation of the folds is not present. The benign ulcer is often discrete, sharply outlined, deep, and always visualized, while the neoplastic ulcer is often shallow, irregular, and less well defined. The benign ulcer is central in relation to the inflammatory mass and the surrounding folds are unsharp and edematous. If the ulcer is at the apex of the bulb, the resulting spasm proximally and distally produces the "bow-tie" or "butterfly" deformity with ulcer representing the "knot" or "torso" and the inflammatory mass and edema distally and proximally, the flaring ends of the tie or wings of the butterfly. Peptic ulcer angulates and shortens the duodenum.

In neoplasm, the ulcer is often eccentric, irregular, and the mucosal folds nodular, irregularly widened, or sharply cut off (amputated) or drawn out due to infiltration.

A long history of peptic ulcer should alert the physician to the possibility of ulcer as a possible cause for jaundice (1). All our cases had a history of ulcer and two a history of upper gastrointestinal bleeding prior to onset of jaundice.

Morphine study or hypotonic duodenography may help in separating neoplastic mucosal fixation from spasm associated with peptic ulcer.

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Adolescent Psychiatry in a Foster Care Residence: Future Directions

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The have-nots are a matter of increasing concern on the current social scene and are of particular interest to the community psychiatry movement. Their deprivation can be measured along a variety of dimensions, among which are socioeconomic and familial supports. Mac Lennan (1) has written about approaches to treatment of socially deprived youth, and Katz (2) has published on the problems of foster children. The thoughts of both these authors are applicable to the subjects of this report, a group of adolescents, whose families of origin occupy positions at the lower end of the socioeconomic scale, and who are in foster placement at a group residential setting. They will be described in terms of their demographic characteristics, backgrounds, psychiatric diagnoses, and utilization of treatment services. The data will form the basis of recommendations relative to the future deployment of a scarce resource—the time of psychiatrists engaged in providing services to youngsters in institutions.

The Lt. Joseph P. Kennedy Jr. Home is located in a middle class neighborhood in the Bronx, New York City. It has been open for more than twenty years, providing care away from home for boys and girls of the Catholic faith. Approximately two hundred school age children are in residence, living in groups of about fifteen members apiece, each group in an individual cottage.

Psychiatric services are provided on a outpatient basis in a clinic located on the grounds of the agency. The staff of psychiatrists and clinical psychologists are employed part-time by the Kennedy Home. During the year 1970, forty adolescents were seen by the author for complete psychiatric evaluation, consisting of a review of all available records and behavioral observations, including results of a standard battery of psychological tests, and clinical interview of one to two hours duration with mental status examination. Psychotherapy was offered where indicated. Subjects were followed for one year from the completion of the diagnostic study with reference to their utilization of psychiatric services. The number studied is about one-third of the adolescent population in residence. It may be that the sample is not entirely representative of all youngsters referred to the clinic, and it is not claimed to be descriptive of the general population of the Home.

Description of the Subjects

Twenty-five girls and fifteen boys were evaluated. Of the forty members of the sample, 18 were Caucasian, 16 Spanish (primarily Puerto Rican), and 6 black. All were between 13 and 17 years of age, with an average of 15.5 years. Their mean level of education was 9.3 years; more than three-quarters were in the ninth or tenth grades.

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Total length of placement prior to consultation varied from a few days to more than fourteen years, averaging 5.4 years. Only three of the teenagers were in placement for less than a year, and if they are eliminated from the calculation, the remaining 37 average 5.9 years of institutional living. One-eighth have been way from home for more than a decade, and over half for longer than five years. Seventeen of the subjects have had all of their foster care at the Kennedy Home; the other 23 have resided in from two to five different agencies, with a mean of 2.8 agencies.

Initial placement away from home was because of inadequacy of the parent(s) in the majority of cases, with the remainder being judicially determined neglect, mental hospitalization of the parent, or desertion. Well over half of these younsters came from one-parent families, and for 29 out of the 40, father was absent from the home.

Intelligence was measured for each subject by one of the staff psychologists, using the age-appropriate Wechsler scale. The average full scale I. Q. of the adolescents was 89.7 (range 57–118), which is approximately the 25th percentile. Only 10% of the sample scored over 100. The mean verbal I. Q. was 86.2 (range 61–114), almost one full standard deviation from the mean of the general population and at less than the 20th percentile. Only one of the subjects scored over 100 on this measure. Even in this group's stronger area, that of performance I. Q., their mean score of 95.6 (range 61–125) is exceeded by about 60% of the population at large.

Referral and Outcome of Consultation

Referral for psychiatric services could be initiated by any member of the Kennedy Home staff, if they had adequate reason to suspect the existence of problems amenable to intervention. Each program department (e.g., child care, social service, education) at the agency was then asked to submit its observations and evaluation of that individual to the clinic prior to the first appointment. Almost two-thirds (n = 26) of the sample were referred because of what can best be termed misbehavior and maladjustment. An example of an actual presenting writeup for one subject included the comments, "school truancy . . . fresh and defiant to staff . . . ignores rules and regulations . . . not following restriction . . . telling lies." In substance then, their probelms were largely disciplinary in nature. Twenty percent were seen for problems not easily classified, such as "moodiness," "seeks father image," or "refuses to visit family." Four were sent to clinic because of a prior history of psychiatric contacts, while only two of these 40 adolescents referred themselves for treatment.

Since all diagnoses were made by the author, an explanation of the criteria used is in order. It should also be noted by way of partial elimination of the criticism of bias, that all evaluations were completed prior to the decision to report on the population. None of these adolescents was classified as psychotic; all were free of indications of thought or affect disorder on clinical interview and projective tests. Similarly, classically neurotic syndromes were conspicuous by their absence. Overt anxiety and depression were virtually nonexistent; the outstanding characteristic of these children was acting-out rather than internalization of affect. No phobic, obsessional, dissociative, conversion, or hypochondriacal symptoms were seen. This leaves us with two broad categories—adjustment reaction, plus the personality and behavior disorders, hereinafter referred to as character disorders. The latter conditions were diagnosed only if the maladaptation was more than a year in duration and involving multiple areas of function, e.g., school, work, peer relationships, use of leisure, or response to authority. This is an operational definition. It is recognized that some of the behavior is evidenced because of the abnormality of the living situation (i.e., the institutional milieu), and that perhaps, under different circumstances, a percentage of these adolescents would not be so labeled. If both criteria did not apply, and pathology was detectable, the diagnosis of adjustment reaction was assigned.

Half of those seen received a diagnosis of character disorder. Of the remainder, fourteen were considered to be undergoing an adjustment reaction of adolescence, but in five of these cases the qualifying phrase, "mild" was added. No diagnosis could be made for six of the subjects, so that total of 11 (27½ percent) were really free of significant psychopathology. Neurotic features were noted in four of the youngsters with adjustment reactions. There was no correlation between age or length of placement and diagnosis. Because of the fluidity of defenses in this age group, and the fact that mixed pictures of pathology were frequent, no specific subgrouping is attempted. The common reactions were passive-aggressive, hysterical, antisocial, and schizoid. Looking at the reasons for referral as related to diagnosis, those in the misbehavior-maladjustment group were considered to be ill in 25 of 26 cases (17 character disorder, 8 adjustment reaction). The other groups are too small in number to permit any meaningful conclusions.

Psychiatric treatment was offered to 26 of the 40 subjects; all of the 20 persons with character disorders and six with adjustment reactions. Eight of these youngsters categorically refused further contact with the clinic, all except one diagnosed as having a character disorder. Nine individuals began therapy, but rapidly established a regular pattern of nonattendance, and within two to three months discontinued coming entirely. Thus, 17 out of 26 (65.4 percent) did not make use of available treatment services. Of the nine who became engaged in the process of psychotherapy, two left the institution within a few months, two more had to be transferred to other facilities for more intensive treatment, and one attended irregularly for just under a year, leaving only four to complete a full year of outpatient therapy. This represents but ten percent of the youngsters evaluated. While again many of the numbers are too small to permit any generalizations, one additional interesting and pertinent observation emerges. Of the 17 to whom treatment was offered but not accepted, 16 were in the misbehavior-maladjustment group. Less than half of those who availed themselves of therapy were referred for such reasons.

Discussion

We are immediately confronted with the problem of motivation for psychotherapy. Rogers (3) has reported on the "unmotivated" adolescent who wants therapy, and she notes that refusal of treatment is often used to demonstrate activity, as opposed to passivity, on the part of the prospective patient, who rarely initiates the request for consultation. In her sample, youngsters of markedly different circumstances, a large number disappeared and then returned on their own motivated for involvement with the therapist, asserting this as their own choice. In the current population, this phenomenon was observed but once, although a few of the subjects not utilizing offered treatment maintained occasional friendly contacts with the clinic. At least a part of the explanation for this discrepancy is the peer group pressure at the institution to avoid the label of "crazy" automatically applied to anyone seeing a psychiatrist. The grapevine was such that all of the students seemed to know precisely who attended the clinic. Thus, a great deal of determination was necessary for one to get the required psychotherapeutic assistance.

That treatment efforts will be rewarded is evidenced by data collected by Graffagnino et al (4). Working with latency age children in an inner city therapeutic school, youngsters from unstable homes of low socioeconomic status, they found that over half of the children presenting with disruptive, aggressive, and impulsive behavior had internalized, psychoneurotic conflicts, responsive to treatment. This tendency for patients with characterologic problems to appear more neurotic as treatment progresses is not unknown, and was seen in the subjects of the current report as well.

Some of the current findings are sobering, and at the same time disturbing in light of recent research. Much passive-aggressive behavior was noted in the group studied. Small and associates (5), in a long-term follow-up of adults so diagnosed, showed that the majority have persisting psychiatric difficulties (although not incapacitated) and only a small percentage are symptom free. Robins' group (6), affirming for blacks their earlier findings with a white population, demonstrated that juvenile antisocial behavior is a very strong predictor of adult disorders within what they term the, "antisocial spectrum." Among the most important indices were school absences and failures, aggressive behavior, father's absence from the home, and low socioeconomic status. The subjects of the present report are adolescents with all of these problems.

Conclusions and Recommendations

In the population described in this paper, institutionalized adolescents of low socioeconomic status, individual psychotherapy reaches only a small percentage of those for whom it is deemed indicated. This type of service must continue for youngsters willing to participate actively in the treatment process. But what about the majority, those who do not elect to avail themselves of this form of assistance? Certainly such a large number of people cannot be written off as simply unamenable or unmotivated. Perhaps other modalities should be made available to them. Conceivably, group approaches will prove more palatable to some of these prospective patients. This affords an additional avenue, but does not address itself to the very large problem of the resistances encountered to any kind of continuing psychiatric contact in this group. They are vulnerable to dysfunction, and at some level of consciousness, equate therapy with the presence of serious psychopathology, something which is feared and defended against with great tenacity.

What, then, can be done? Other helping disciplines, in this case the child care worker, are the primary care-givers. They are in daily contact with the children, and their functions encompass all of the day to day activities and routines of the child's life. This group is striving for increased professionalization. They will undoubtedly achieve increased importance and responsibility in the future, with the proliferation not only of settings such as described here, but also in schools, day care centers for children of working mothers, and other programs of the antipoverty efforts of our nation. Clinical psychiatrists have much to offer to child care workers and must become actively involved with their education and training, through lectures, seminars, groups, and other modalities.

Relative to productivity of psychiatric services within the institution, the data reported herein support the conclusion that traditional one-to-one psychotherapy is not the most valuable allocation of the consultant's time. These findings are likely applicable to a variety of residential settings in addition to the specific facility described. Consultation and education is one of the five essential services of a federally assisted community mental health center. It may be assumed that more and more social agencies will call upon such centers as they proliferate and the availability of their services becomes better known to their communities. While these providers of care may often request direct services for their troubled clients, it seems more judicious to explore other possibilities as well. By changing the focus from direct treatment to indirect services, more patients can benefit. With a knowledge of the particular institution, its staff, and those it exists to serve, the psychiatrist is in a position to aid in the growth and development of all three by providing an increased understanding of human behavior and its meanings, as applied to individuals and groups. In essence, what is proposed is an ongoing program of in-service education addressed to the primary care givers, based on consultation to staff centering around the individuals in their charge. In this fashion, their role as the active helper is enhanced, and the consultant's available hours are put to better use than waiting for patients who do not keep their appointments, or otherwise reject therapy.

As various agencies and institutions come to employ psychiatrists as staff members, their administrators, and, just as importantly, the funding sources which provide for the salaries of clinical personnel, must be made aware of the fact that services to staff are really services to the clientele. Indeed, they can reach larger numbers and greater percentages of the target population heretofore untouched by psychiatric expertise. In this fashion, also, the present and future goal of primary prevention of psychiatric disability in highly vulnerable individuals can be better approximated.

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Red Cell Defects in Fanconi's Anemia*

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Defects in the red cells and in erythropoiesis which may cause progressive anemia in children with Fanconi's anemia have been mentioned in the literature but are not consistently found (1). We recently observed a child with Fanconi's anemia who showed several physiological and biochemical red cell defects, some of which have not been previously described in this disease.

Case Report

An extremely small 6-year-old Negro boy was admitted to the Nassau County Medical Center for study because of short stature and anemia. He was the product of a full-term pregnancy and normal delivery; birth weight was 5½ pounds; length was 17 inches. Development was normal. An umbilical hernia was repaired at 5 years of age. The parents and all four siblings were normal. The family history was negative for congenital anomalies and blood diseases. The child weighed 30½ pounds and was 39 inches tall. Sprengel's deformity was present. The thumbs were short and the thenar eminences were flat.

Blood count showed a hemoglobin level of 7.3 gm; hematocrit, 22.5 percent; and white blood cell count 2,800/mm^3, with 80 percent lymphocytes. The red cells were macrocytic and many cell fragments were present. The MCV was 100 cμ (normal 84–94), MCH and MCHC were normal. Platelet count was 35,000/mm^3 and the platelets on smear appeared unusually small. Numerous serum chemical determinations were normal. The tryptophane loading test showed normal urinary excretion of kynurenic and xanthurenic acids. Metapirone test and growth hormone assays indicated primary growth hormone deficiency (2).

X-ray of the cervical spine showed fusion between C-5 and C-6, and occipitalization of C-1 (Klippel-Feil anomaly). Intravenous pyelogram showed crossed renal ectopia, with both kidneys on the right side. Chromosome analysis of peripheral lymphocytes showed the male karyotype of 46XY. However, structural damage and/or rearrangements were seen in 60 percent of the cells examined (2). Bone marrow aspiration initially showed normal erythroid and myeloid elements. Repeat examination 12 months later showed marked hypoplasia. Accordingly, the reticulocyte count when the child was first seen was 2.0 to 2.5 percent, but 12 months later it ranged from 0.2 to 0.4 percent. Urinary and serum erythropoietin were greatly increased on two in vivo assays done at an interval of eight months. Efforts to detect presence of an erythropoietin inhibitor were unsuccessful. The Cr^{51} red cell T-½, plasma Fe^{59} clearance T-½, and Fe^{59} incorporation were all normal. On isotopic scan of the liver and spleen there was normal size and configuration of both organs.

Human growth hormone, 2 International Units, was given subcutaneously three times a week. Determination of hematocrit, white blood cell count, platelet count, and reticulocyte count were done daily at first and then weekly. By the end of 12 months of growth hormone therapy the child's height increased to 41½ inches (a gain of 2½ inches) and the weight to 34 pounds (a gain of 3½ pounds). But there was a continued fall of the hematocrit, requiring five blood transfusions, and the platelet count fell to 10,000/mm^3.

Red cell osmotic fragility, using the Fragiligraph (Kal-Medic®) method (3), showed a distinct *increase* in resistance of the patient's red cells to osmotic lysis (Fig. 1). The patient's red cell membranes were solubilized and studied by acrylamide gel electrophoresis. Differ-

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ences were observed between the solubilized components of normal red cell membranes and red cell membranes of our patient (Figure 2). The patient showed an extra band. Both electrophoresis and chromatography showed hemoglobins F, A, and A_2. Hemoglobin A_2 was 1.25% by DEAE-Sephadex chromatography (4) (normal adult range 2.2–3.0%). Hemoglobin F was 26 percent (5, 6). No increase in hemoglobin F was observed upon electrophoresis of hemoglobin from the mother and siblings. Hemoglobin F was examined chemically (7) in order to determine the ratio of $G\gamma$ to $A\gamma$ chains. This ratio averages 3:1 in the newborn infants and 2:3 in the older child and adult (8). In the patient, the ratio of 2:1 places the result within the range of the newborn child. Betke stain showed unequal content of hemoglobin F in the red cells (Fig. 3). Red cell G-6 PD, glutathione reductase, and pyruvate kinase were all normal. Hexokinase was slightly elevated. Serum ceruloplasmin, serum copper, and serum iron were all slightly increased. Serum haptoglobin was slightly decreased. As he entered the phase of bone marrow failure, the patient showed macrocytosis and megaloblastoid changes in his neutrophils, metamyelocytes, and normoblasts. Serum folic acid was 5 ng/100 ml (normal 4–16) and the serum vitamin B_{12} was 920 pg/100 ml (Normal 150–710). The urinary excretion of formiminoglutamic acid (FIGLU) and methylmalonate were normal.

Comment

The various skeletal, renal, cytogenetic, hematopoietic, and endocrine abnormalities present indicated that this child has Fanconi's anemia and primary growth hormone deficiency (2).

Does this child have increased hemolysis of his red cells? The red cell life-

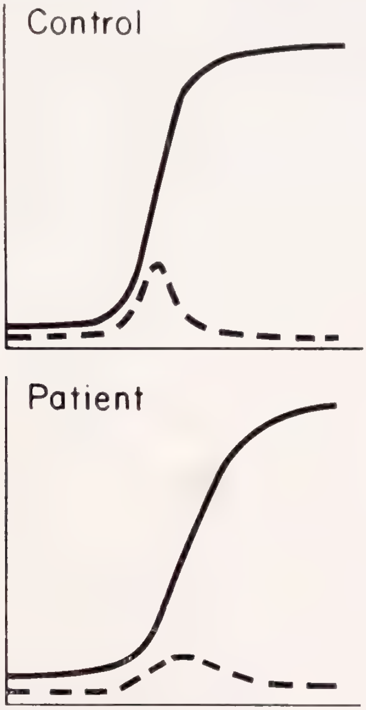

FIG. 1. Fragiligram curves showing increased resistance of the patient's red cells to osmotic lysis. Broken lines are derivative curves.

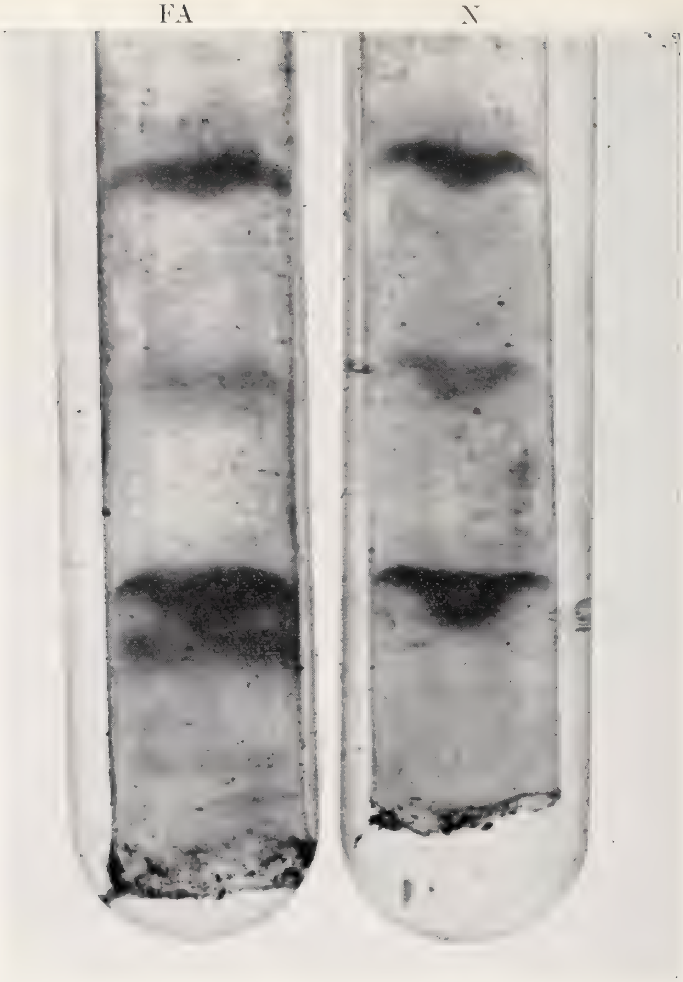

Fig. 2. Acrylamide gel electrophoresis showing difference of solublized components between normal red cell membranes (N) and red cell membranes of the patient with Fanconi's anemia (FA).

span of our patient was normal, and it would seem that excess hemolysis plays no role in the pathogenesis of the anemia. However, Cr^{51} measurements only measure the survival of cells whose viability is measured in days. It is quite possible in these patients that many grossly defective cells (cell fragments) are delivered into the circulation which survive for only a matter of minutes or hours (9, 10). These cells are not detected by present methods. Hemolysis of defective red cells (ineffective erythropoiesis) may therefore be more important than is at first apparent.

The red cell membranes in our patient with Fanconi's anemia differed physiologically and biochemically from normal red cell membranes; they showed a fragiligram (Fig. 1) with more gradual cumulative curve and a flatter deriva-

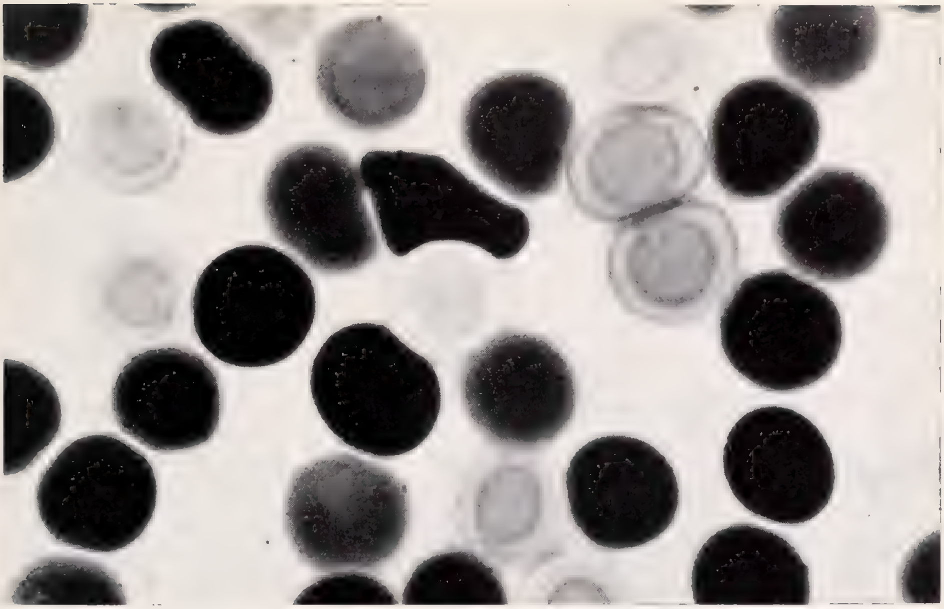

FIG. 3. Blood smear stained by the Betke method for hemoglobin F, showing unequal content of hemoglobin F in the red cells.

tive curve, due to the presence of an osmotically more resistant red cell population. This finding is suggestive either of an abnormally young population of red cells or a red cell membrane which has increased resistance to osmotic lysis (3). The greatly increased hemoglobin F in the red cells may have caused increased resistance to hemolysis since the fragility test was done at a slightly alkaline pH. Fragiligraph curves of newborn red cells are similar to the patient's. These findings suggest that in addition to bone marrow hypoplasia there is hyperhemolysis of peripheral erythrocytes. The cause of the increased rate of hemolysis would appear to be intracorpusucular factors, since no antired cell antibodies and no evidence of hypersplenism could be found. In addition to these physiologic differences between normal red cell membranes and those of our patient with Fanconi's anemia, chemical differences were detected by acrylamide gel electrophoresis. (11, 12)

This patient has a very low level of hemoglobin A_2 and the hemoglobin F present chemically resembles that of the newborn rather than that usually found in older children. The hemoglobin A_2 level is also very low in the newborn. It thus appears that this child with Fanconi's anemia may have partially reactivated (or failed to "switch off") the mechanism that permits hemoglobin F production and inhibits hemoglobin A_2 production in the fetus and newborn. Hemoglobin F is commonly elevated in children with Fanconi's anemia, but the level is rarely as high as it was in the case presented here (1, 13, 14).

This case of Fanconi's anemia is very unusual in that he also has primary growth hormone deficiency. Because of this we were able to give him a prolonged course of human growth hormone. During the 12-month period of growth hormone administration the child grew a significant amount, but the blood count was not improved, in fact, it continued to fall. It was observed by others that growth hormone administration causes increased erythropoiesis in hypophysectomized rats (15) and in dogs (16). But growth hormone administration did not stimulate erythropoiesis in our child with growth hormone deficiency. The serum and urinary erythropoietin levels of our case were elevated, suggesting that bone marrow failure is not due to lack of hormonal stimulation, but due to end organ failure (17).

Summary

A child with Fanconi's anemia showed several intrinsic red cell defects. There was an abnormally low level of hemoglobin A_2 and marked elevation of hemoglobin F. The hemoglobin F was chemically similar with that seen in newborn infants, rather than that seen in older children. Red cell osmotic fragility was decreased. Acrylamide gel electrophoresis of the solubilized red cell membranes showed differences from normal red cell membranes. These data suggest that intrinsic red cell defects may be contributing causes of the anemia of Fanconi's anemia. Administration of human growth hormone for 12 months caused increase in somatic growth but did not alter the hematopoietic failure.

Acknowledgments

Erythropoietin assays were done by Dr. Albert Gordon, New York University. Special hemoglobin F studies were done by Dr. Titus Huisman, Medical College of Georgia, and Dr. William Schroeder, California Institute of Technology. Red cell enzyme studies were done by Dr. Ernst Jaffé, Albert Einstein College of Medicine.

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The Use of Glucagon and Isoproteronol in the Evaluation of Isolated Pulmonary Stenosis

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Introduction

The effect of glucagon on hepatic glycogenolysis and its therapeutic usefulness in the treatment of hypoglycemia is well recognized (1, 2). That this agent can exert profound effects on other organs and systems, however, is only now being appreciated. Recently, interest in the actions of this agent have centered on the cardiovascular changes which it may produce. It has been observed that glucagon produces both positive chronotropic and positive inotropic effects on isolated cardiac muscles, in heart–lung preparations, and in the intact animal (3, 4). In addition, Parmley and coworkers have reported that glucagon produces similar effects in man (5).

To provide further information regarding this potentially useful action of glucagon in the congenital heart disease, especially in the evaluation of patients with pulmonary valvular stenosis, the following study was performed:

Methods

Six children and young adults, aged 8 to 17 years, with isolated congenital pulmonary valvular stenosis were studied during routine diagnostic cardiac catheterization. The pertinent clinical features are summarized in Table I.

A double lumen catheter placed in the pulmonary artery and the right ventricle permitted simultaneous recordings of pulmonary arterial and right ventricular pressures. Brachial artery pressure (BA), right ventricular (RV), pulmonary artery (PA) pressures, the first derivative of right ventricular pressure dP/dt and lead II of the electrocardiogram were recorded on a multi-channel Electronics for Medicine® photographic recorder. Cardiac output was measured in duplicate by the dye dilution technique.

Control observations were made in the fasting basal state without premedication. Moderate supine leg exercise was performed using a bicycle ergometer at a work load of 54 foot pounds per minute in the supine position for seven to ten minutes. During exercise, pressures were recorded and cardiac outputs determined.

After returning to the basal state, all patients then received a constant infusion of isoproteronol 0.3 to 0.7 micrograms per kilogram per minute which was regulated to produce the same heart rate achieved during exercise. A stable peak effect was noted after two to four minutes. Pressure measurements and cardiac output were repeated. Toxic symptoms attributable to this drug were not encountered, apart from an occasional ventricular premature beat. Sixty

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TABLE I
Summary of Patients Studied

Patient	Age, Sex	Symptoms	Chest X-ray	ECG	Cardiac catheterization, gradient PA to RV
1. P. G.	12 yrs. M	Fatigue	Moderate Cardiomegaly	RVH	65 mm Hg
2. S. T.	8 yrs. M	None	Normal	RVH	55 mm Hg
3. T. R.	10 yrs. M	None	Normal	RVH	48 mm Hg
4. P. S.	13 yrs. F	Fatigue, Dyspnea	Mild Cardiomegaly	RVH	60 mm Hg
5. G. R.	9 yrs. M	None	Normal	RVH	35 mm Hg
6. A. S.	17 yrs. M	Fatigue	Mild Cardiomegaly	RVH	52 mm Hg

minutes after the isoproterenol infusion was discontinued, heart rate, systemic arterial pressure, and right ventricular pressure had returned to the basal control study level. Four or five mg of glucagon were then injected intravenously over approximately 30 seconds. Pressures, right ventricle dP/dt, cardiac output, blood sugar, and blood potassium were then recorded 5, 15, 30, and 60 minutes following glucagon administration. The incidence of vomiting following glucagon infusion in our study was insignificant. One patient experienced nausea and vomited once. However, because of possible consequences of this undesirable effect, routine intubation may be advisable in all anesthetized or heavily sedated patients. Continuous oscilloscopic monitoring was carried out in all patients during cardiac catheterization. No arrhythmias or other toxic effects were observed following injection of glucagon in this study.

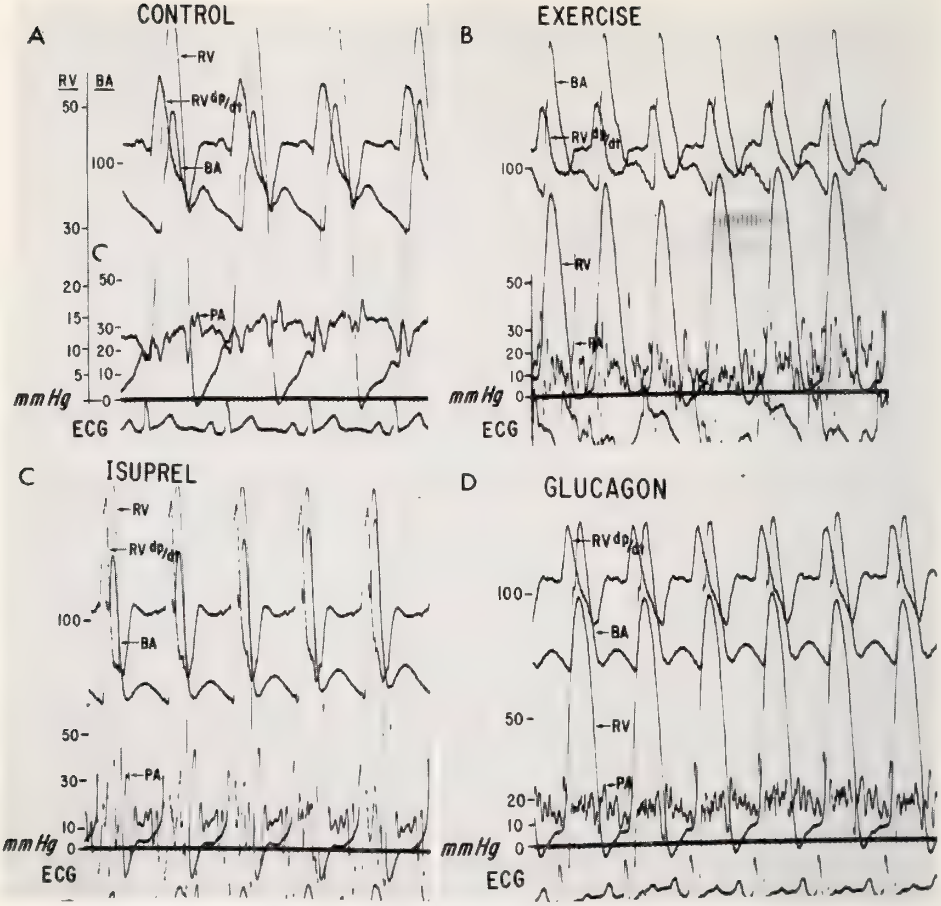
Results

Figure 1 shows the typical hemodynamic effects observed following exercise, infusion of isoproterenol, and a single dose of 4 mg of glucagon. The patient is a 12-year-old boy with moderate pulmonary valvular stenosis.

Figure 2 summarizes the hemodynamic effect of exercise, isoproterenol, and glucagon in six patients with pulmonary valvular stenosis.

The heart rate increased during exercise from a mean of 79 per minute to a mean of 122 per minute and the gradient across the pulmonic valve rose 64 percent. Right ventricular dP/dt doubled, cardiac output and cardiac index rose approximately 75 percent. No significant changes in right ventricular end diastolic pressure, systolic, or mean systemic pressures were noted. Pulmonary artery systolic and pulmonary artery mean pressures increased slightly.

The response to isoproterenol stabilized following two to four minutes of infusion. The heart rate increased in all six subjects, rising from a mean of 79 to a mean of 125 per minute. The gradient across the pulmonic valve rose 114


A
CONTROL
RV
BA
50
RV dP/dt
100
BA
30
C
20
50
15
30
10
20
5
10
mm Hg
0
ECG
B
EXERCISE
BA
RV dp/dt
100
RV
50
30
20
PA
10
mm Hg
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ECG
C
ISUPREL
RV
RV dp/dt
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GLUCAGON
RV dp/dt
100
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FIG. 1. A significant increase in heart rate, right ventricular pressure (RV) and right ventricular dP/dt was noted in each study following exercise, intravenous infusion of isoproterenol and glucagon.

percent when compared to the resting gradient. Mean pulmonary artery pressure rose slightly, 14 percent, while the systemic arterial pressure fell as did the systemic vascular resistance. Right ventricular dP/dt rose 217 percent and cardiac output 89 percent when compared with control values. No significant changes in right ventricular end diastolic pressure were recorded.

Peak effects of glucagon were observed by five minutes and the patient had returned almost to the control state 15 minutes following the infusion. At five minutes following the administration of glucagon, an increase in mean heart rate from 79 to 124 occurred. Systolic gradient across the pulmonic valve rose 69 percent, right ventricular dP/dt 124 percent and cardiac output rose 75 percent compared to the control state. There was a slight increase in pulmonary artery systolic and pulmonary artery mean pressure, 12 percent, without appreciable effect on aortic systolic or aortic mean pressure.

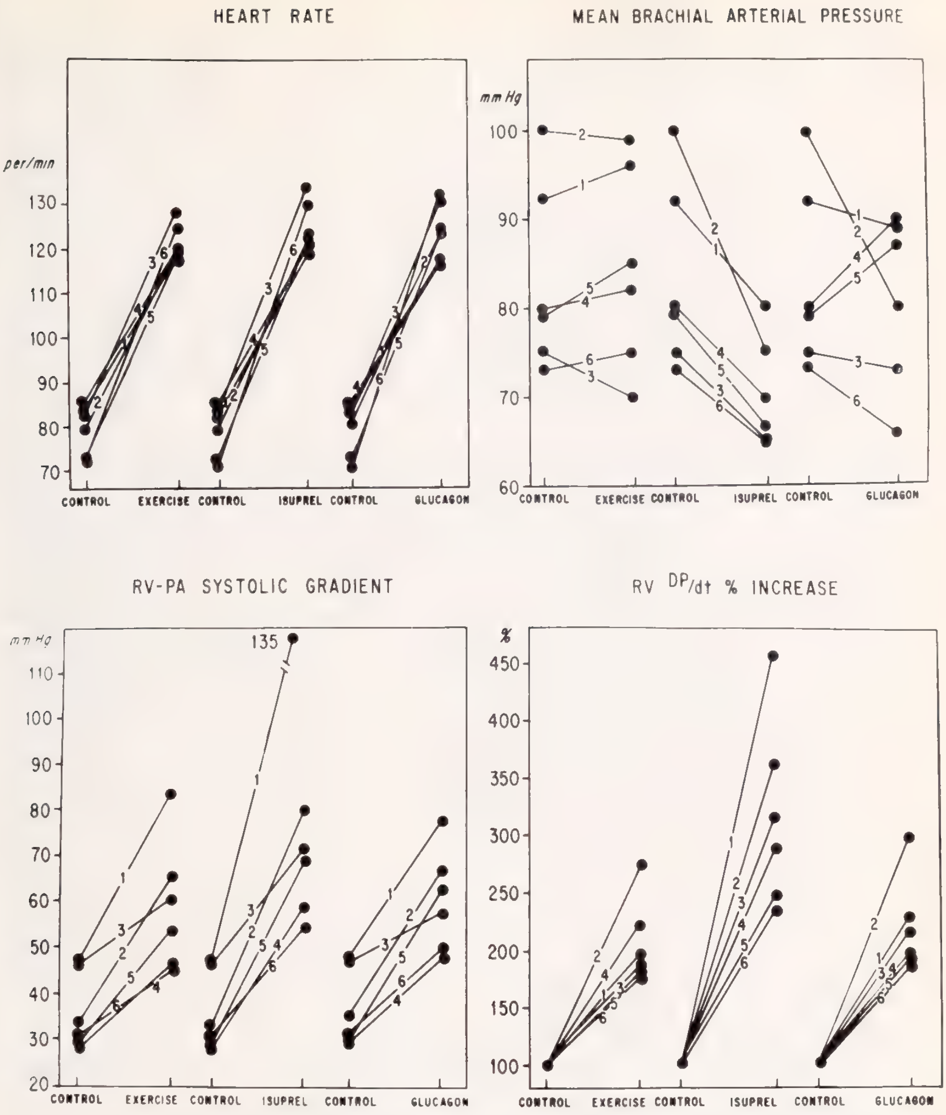

FIG. 2. Summary of hemodynamic changes in patients with pulmonary vascular stenosis following exercise and infusion of isoproterenol and glucagon.

The ability of glucagon to increase contractility in these patients without overt heart failure was manifested by an increase in RV pressure, dP/dt, and cardiac index, at a constant right ventricular end diastolic pressure. This study confirms previous experience of a significant positive inotropic and chronotropic effect of glucagon (2).

Blood sugar increased an average of 50 percent following glucagon infusion whereas serum potassium simultaneously fell from 4.2 to 3.8 per liter. This decrease in serum potassium presumably resulted from insulin response to hyperglycemia and the subsequent movement of glucose and potassium into cells.

Discussion

This investigation confirms previous reports on the physiological effects of glucagon and is the first reported application of its usefulness to simulate exercise clinically. Accurate assessment of the functional severity of isolated pulmonary valvular stenosis during cardiac catheterization requires the measurement of the pulmonary ejection gradient during both the resting and exercise states (6). What may appear as relatively mild pulmonary stenosis in the anesthetized resting patient may in fact represent a considerable stress to the right ventricle during the routine activity of daily life. The effect of exercise on the pressure gradient across the stenotic valve can usually be assessed in the adult without much difficulty, but in infants and children who require sedation or anesthesia for cardiac catheterization this is not usually possible. Those children who are sufficiently aware are generally unable to comprehend or to carry out instructions and do not tolerate prolonged studies. Since most of the cardiac catheterization studies are now performed in these younger age groups, the assessment of the pressure gradient under physiologic conditions is not usually possible. The purpose of these investigations was to attempt to reproduce the physiological alterations of exercise in patients with congenital isolated pulmonary stenosis by the intravenous infusion of the synthetic catecholamine isoproterenol and the hormone glucagon. Both of these drugs are known to produce chronotropic and inotropic effects similar to those of exercise. Isoproterenol and glucagon have had wide clinical usage in the past and have been shown to be safe when administered in appropriate dosage.

The data obtained from these studies revealed a striking hemodynamic similarity between the hemodynamic effects of exercise and glucagon. The effects on cardiac index, stroke index, mean ejection pulmonary gradient, and right ventricular dP/dt were quite similar. No significant changes in right ventricular diastolic pressures or mean pulmonary artery pressure were noted. In comparison, there were some discrepancies between the effects of exercise and isoproterenol. Isoproterenol produced a fall in the arterial pressure and systemic vascular resistance beyond that noted following exercise and glucagon infusion. In addition, cardiac index, RV pressure, dP/dt, and pulmonary ejection gradient exceeded significantly those observed during exercise and following glucagon at the same heart rate.

In conclusion, these studies indicate that infusion of glucagon is a safe, practical, and effective means of simulating exercise in infants and children. Used in addition to the customary cardiac catheterization studies it is of distinct value in appraising the severity of pulmonary valvular stenosis.

Summary

The maximum hemodynamic effects of moderate exercise, isoproterenol, and glucagon were evaluated in six patients with moderate congenital pulmonary valvular stenosis at equal heart rates. An increase in RV, dP/dt, cardiac index, and systolic pulmonary gradient were noted in each case. However, isoproterenol produced a significant decrease in aortic systolic pressure and had signifi-

cantly greater inotropic effect than exercise or glucagon. The hemodynamic effects of glucagon closely simulated those of moderate exercise, and its use, therefore, is suggested as a means of evaluating the dynamic aspects of pulmonary valvular stenosis in infants and children.

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OPHTHALMOLOGIC NOTES

THEODORE W. LIEBERMAN, M.D., Editor

Retinal Cotton Wool Spots and Cytoid Bodies

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Clinical Features of Cotton Wool Spots

The ophthalmoscopic appearance of retinal cotton wool patches is well known to the physician. These lesions occur in a variety of diseases, most notably vascular hypertension, the "collagen" diseases, central retinal vein occlusion, diabetic retinopathy, papilledema, the dysproteinemias, leukemia, and severe anemia (1). On ophthalmoscopic examination one or more (but usually less than 10) cotton wool spots are seen. They occur preferentially in the posterior portion of the retina, rendering them readily detectable by casual examination. The optic nerve head is often involved. Each cotton wool spot appears as a grayish-white, soft, fluffy exudate, usually more closely related to the arterioles than to the veins, lying in the inner layers of the retina and bulging slightly toward the vitreous body (Fig. 1). They are small, averaging about one-third of a disc diameter in width. (The normal diameter of the optic nerve head is from 1.5 to 2.0 mm.). Cotton wool spots usually clear within one to three months of their appearance.

Pathologic Features of Cotton Wool Spots

Pathologic examination of a cotton wool spot confirms the clinical impression that the lesion involves chiefly the inner layers of the retina (Fig. 2). The ganglion cell nerve fiber layer is greatly thickened in a disciform, sharply circumscribed fashion. In this region some of the nerve fibers are interrupted and in many cases "cytoid bodies" are seen (Fig. 3). The latter are globular bodies 10 to 20 microns in diameter (2). Each bears a superficial resemblance to a cell because of a centrally located structure simulating a nucleus (Fig. 4). But unlike the typical nucleus, these centrally located structures do not contain DNA and are eosinophilic, rather than basophilic. They contain lipid and they stain intensely with Schiff's periodic acid technique.

The nature of these cytoid bodies has been argued since their discovery in 1856. Heymann was the first to recognize them (3). He regarded the structures as degenerated retinal ganglion cells. In 1858 Müller showed they were swollen and degenerated nerve fibers, rather than degenerating ganglion cells (4). His work was later confirmed by Leber and Koyanagi (5, 6). Subsequently, several alternative views were put forth, one being that cytoid bodies arise from degenerated glial cells, and another that they represent exudates trapped within the

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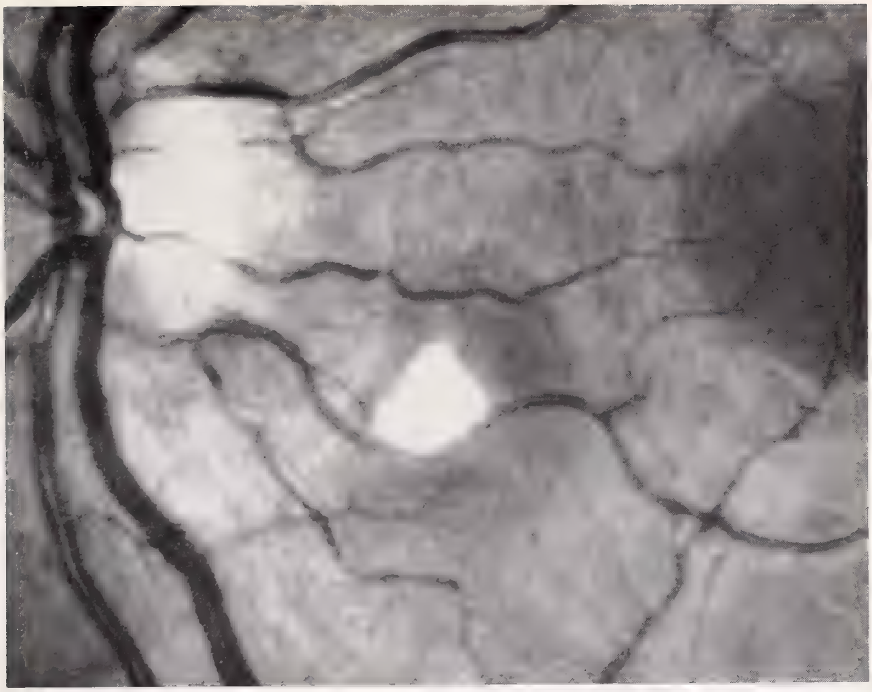

FIG. 1. A typical cotton wool spot in a young woman with systemic lupus erythematosus. The lesion is situated along the upper border of a retinal arteriole, about midway between the optic nerve head and the macula.

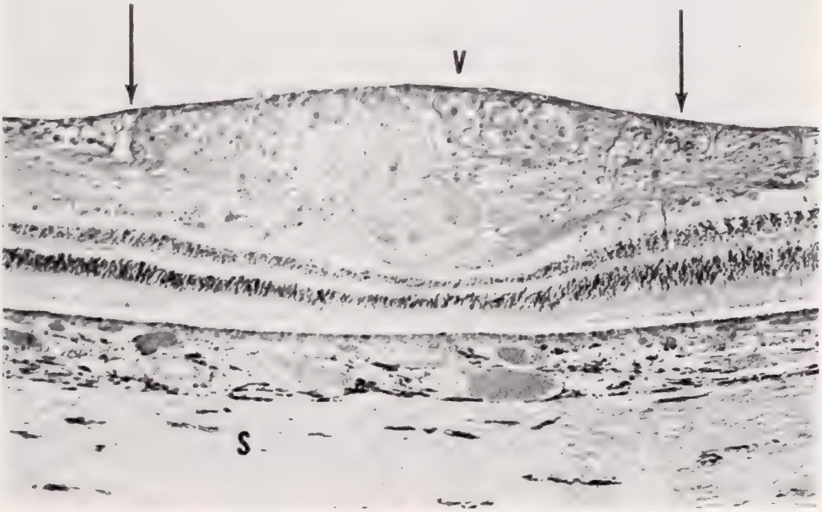

FIG. 2. A cotton wool spot in the retina of a 26-year-old woman who died of systemic lupus erythematosus. The ganglion cell nerve fiber layer is greatly thickened in a disciform, sharply circumscribed fashion (arrows). It bulges internally toward the vitreous body (V), and also externally, distorting the inner nuclear layer of the retina. The rods and cones are separated artifactitiously from the underlying layer of retinal pigment epithelium. S: Sclera. Hematoxylin and eosin; ×76.

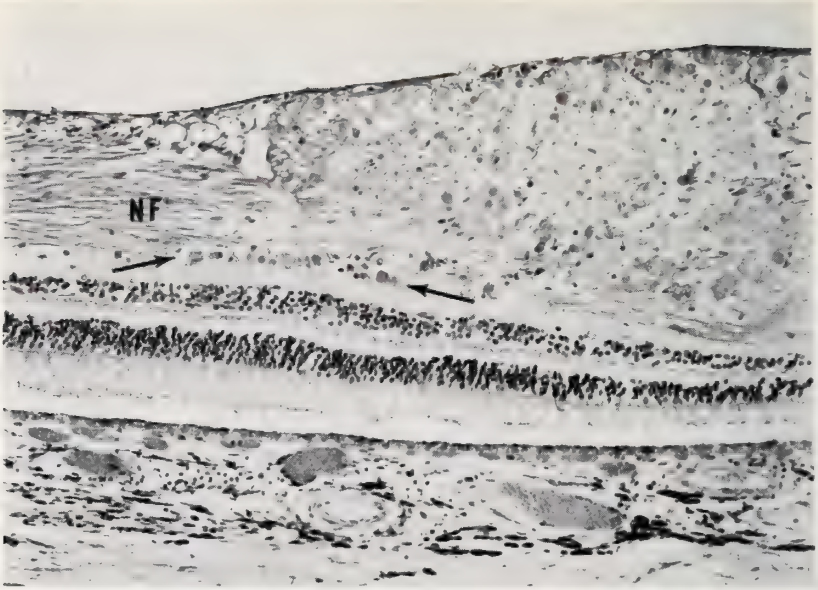

FIG. 3. Same lesion as shown in Fig. 2. Nerve fibers (NF) are interrupted as they enter the area of the cotton wool spot. Many "cytoid bodies" are visible in the lesion. Arrows indicate ganglion cell layer of the retina. Hematoxylin and eosin; ×120.

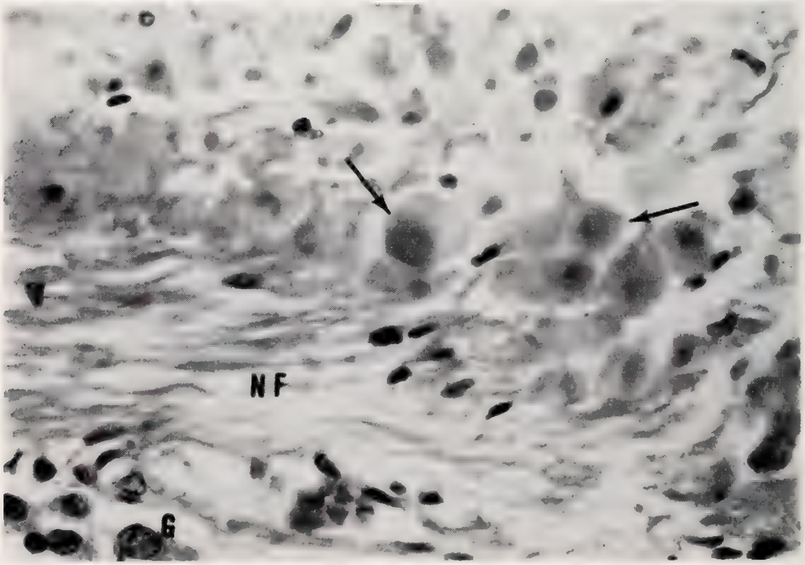

FIG. 4. From near the center of the field shown in Fig. 3. Many "cytoid bodies" are present (arrows). NF: retinal nerve fiber layer. G: retinal ganglion cell. Hematoxylin and eosin; ×480.

glial network of the ganglion cell nerve fiber layer, the pseudonucleus being essentially fibrin and the pseudocytoplasm ground substance (1).

In recent years Wolter has shown conclusively that cytoid bodies arise from the axons of retinal ganglion cells, confirming the earlier work of Müller and other investigators (7, 8). Ashton has reviewed comprehensively the entire problem of the pathophysiology of cotton wool spots (9). His studies with the electron microscope have shown that the cytoplasm of the cytoid body consists of swollen axoplasm containing proliferating mitochondria and neurofilaments, the pseudonucleus consisting of electron-dense material, possibly lipid (9).

Using flat frozen sections of the retina stained with the silver carbonate nerve fiber technique of del Rio Hortega, Wolter demonstrated that some of the nerve fibers were interrupted as they coursed through a cotton wool spot (7). The axonal interruptions were located between the retinal ganglion cell and the optic nerve head. There was prominent terminal swelling of the axonal stumps on the side remaining in contact with the retinal ganglion cells (Fig. 5). On the other side of the interruption (closer to the optic nerve head) there were less numerous, smaller terminal swellings of the nerve fiber stumps.

These bulbous terminal swellings of interrupted nerve fibers on the side continuous with their ganglion cells are not specific to the retina. They are well recognized in neuropathology as a nonspecific reaction of axons to injury. The bulbous swellings are known synonymously as Cajal's end bulbs, terminal swellings, and ganglioform swellings (8). Wolter regards retinal cytoid bodies as being identical with these bulbous terminal swellings, but Ashton believes

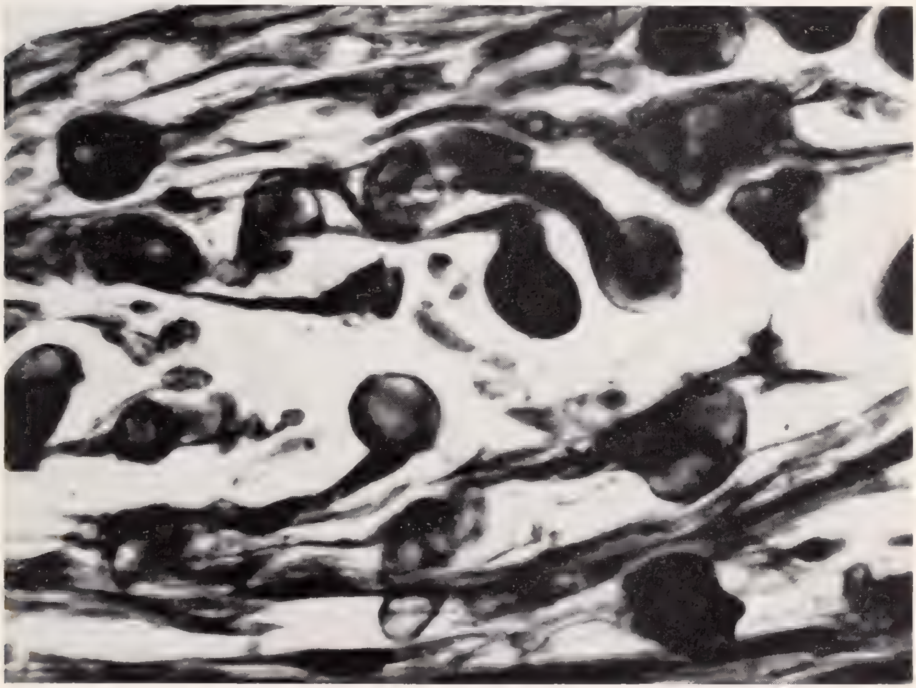

FIG. 5. Nerve fibers exhibit prominent, bulbous terminal swellings of Cajal at site of interruption in a retinal cotton wool spot. The cell bodies of the interrupted nerve fibers are out of the field, to the left. Edema is present between the nerve fibers. Frozen section, silver carbonate nerve fiber technique of del Rio Hortega. (Courtesy of J. Reimer Wolter, M.D. American Journal of Ophthalmology 48:473, 1959.)

that the Cajal bulb is not itself identical with the cytoid body (7, 9). He observes that because there are some instances (diabetic retinopathy) in which Cajal's nodes are common but cytoid bodies unusual, the term "cytoid body" should be used only when the lipid debris of the degenerating axonal structures aggregates to form a pseudonucleus (9).

Pathogenesis of Cotton Wool Spots

It is generally agreed that focal ischemia is the causative factor in pathogenesis of cotton wool spots, but the precise nature of the vascular insufficiency is unsettled. Fluorescein retinal angiography (study of the passage of fluorescein through the retinal circulation after the dye has been injected into an antecubital vein) demonstrates an absence of blood flow in the area of the cotton wool spot. Around this zone of focal ischemia microaneurysms are seen on fluorescein angiography, although they are generally so small that they are not identifiable with the ophthalmoscope (1, 9). If fluorescein angiography is repeated as the cotton wool spot clears, the microaneurysms will be observed to become smaller and eventually disappear.

Pathologic examination of the status of the circulation in cotton wool spots has been greatly facilitated by using retinal whole mounts stained with Schiff's periodic acid technique after the nonvascular retinal tissues have been digested away by pretreatment with trypsin. The lumens of the capillaries in a cotton wool spot are devoid of blood, and their walls exhibit marked loss of endothelial cell and of "intramural pericytes" (1, 9). Further evidence for failure of the circulation in a cotton wool spot has been provided by injecting the blood vessels of retinal whole mounts with India ink, whereupon the capillaries in the lesion fail to fill with the dye (1, 9). Pathologic study of the retina after a cotton wool patch has cleared shows the circulation to be renewed in the area of the former cotton wool patch. This is believed to result from opening of the previously closed capillaries, rather than from the ingrowth of new vessels (10).

The evidence that the capillaries are indeed closed is by no means conclusive, and in pathological specimens they may appear patent although uninjected (9). The term "capillary closure" is used in the sense that their circulation is obstructed, as evidence by failure of the capillaries to become injected with India ink in vitro or to be perfused with fluorescein in vivo (9). The mechanism of capillary closure in cotton wool spots is uncertain, but capillary compression, active capillary contraction, capillary collapse, and endothelial swelling are regarded as factors, either individually or collectively (9).

The cotton wool patch is usually regarded as a microinfarct of the retina resulting from focal ischemia (2). Recently some objection to use of the term "microinfarct" has been voiced (9). But it is generally agreed that the basic cause in each instance is hypoxia resulting from focal circulatory failure. In some cases the ischemia obviously results from obstruction, as in fat embolism, embolism from cardiac valvular vegetations, or experimental injection of artificial emboli. In many other instances the precise mechanism of ischemia is uncertain, but altered capillary endothelial permeability is believed to play a prime role (as in vascular hypertension and the "collagen" diseases) (9). Altered capillary permeability is also thought to be a major factor leading to formation of cotton wool spots in disorders such as pulseless disease where as yet there is no evidence for arteriolar occlusive disease in the retina (9).

Conclusion

Wolter believes the term "cytoid body" is confusing, and that its use should be discontinued (8). One would agree that its use led to a certain amount of confusion, as witnessed by the frequent reference to "cytoid bodies," rather than "cotton wool spot," in describing the ophthalmoscopically observed lesion, both in clinical parlance and in otherwise authoritative textbooks of medicine. Cytoid bodies are histologic components of a cotton wool spot. The two terms are not synonymous. Wolter has emphasized that "cytoid bodies" occur commonly throughout the nervous system and are not something new or specific to the retina. He prefers the term "axonal enlargement" because it "... describes the nature of these products of axonal reaction and is commonly applied by neuropathologists to all parts of the central nervous system" (8). Ashton finds the term "axonal enlargement" not entirely acceptable because " ... a cytoid body is only one stage or type of axonal enlargement" (9).

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NEUROLOGIC NOTES

We inaugurate in this issue a department to be known as Neurologic Notes. This is patterned on the highly successful Radiologic Notes—a popular feature of the Journal since 1956. Similarly patterned Unusual Problems in Surgery and Ophthalmologic Notes followed.

The content of Neurologic Notes will be the responsibility of the Neurological Service, one of the largest and most productive in the country. The format is flexible, the aim is to present in succinct and capsule form observations which should not be lost. The emphasis will be heavily clinical. The House Staff will be particularly urged to contribute. *Editor's Note*

NEUROLOGIC NOTES

Meningiomas Presenting as Large Prominences on the Skull

JOHN LUSINS, M.D. AND ROBERT JAFFE, M.D.

Occasionally, a prominence on the skull, seen as a finding of no consequence, turns out to be due to a meningioma, and may be the only sign of a tumor involving the central nervous system. This report presents four such patients.

Case Reports

Case 1. L.P., a 58-year-old man, was admitted to The Mount Sinai Hospital with the chief complaint of a prominence on the back of the head. It had been there as long as he could remember. He had pointed it out to a number of physicians during examinations for other reasons and had always been told that it was "nothing to worry about." He thought that over the last two years it had become more prominent and it occasionally would feel tender to palpation. On examination he was noted to have a normal mental status and a negative neurologic examination. A large, rounded, hard mass was noted on the back of the head to the left of the midline (Fig. 1). It was not movable or tender (Fig. 1). A left carotid angiogram was performed and a large meningioma was demonstrated.

Case 2. J.E., a 57-year-old man, was admitted with the complaint of poor vision of three months duration. The patient stated that six years previously he had been struck on the right forehead by a wooden box, following which he noticed the presence of a "bump" on his right forehead. This bump had not changed in size over the following six years. For the three months prior to admission he had experienced bilateral blurring of vision without diplopia. On examination he had a normal mental status. On the right forehead there was a large prominence, hemispherical in shape, hard and nonmovable (Fig. 2). The temporal artery on the right side was tortuous and prominent and extended over the lower border of the prominence. The visual fields in left eye showed decrease of vision for color in the nasal portion and for movement in the temporal portion. There was bilateral papilledema with peripheral hemorrhages in both eyes. The gait and coordination was normal. Strength was normal in all extremities. Sensory examination was likewise normal and there were no abnormal reflexes. A left carotid angiogram and a right bracheal angiogram were performed. These demonstrated a large frontal meningioma crossing the midline. This was later confirmed at surgery.

Case 3. P.M., a 19-year-old female, was admitted with the complaint of episodes of numbness and weakness of the left arm and leg for two years. These episodes would last up to 15 minutes and then clear completely. There was no loss of consciousness and occasionally speech was involved. The patient stated that she had a prominent groove along an elevation on the left side of the head which had been present since age 6. On examination, a groove and elevation running in a longitudinal direction for 4 cm was documented. The patient was noted to have normal mental status. There was bilateral engorgement of the discs without exudates or hemorrhages. The remainder of the cranial nerves were normal. Rapid alternating movements were less smooth when performed with the left arm and foot than with the right. Angiography using the left carotid and the right bracheal arteries was carried out and a large vascular meningioma crossing the midline was noted (Fig. 3).

Case 4. A.B., a 51-year-old man, was admitted to The Mount Sinai Hospital with the

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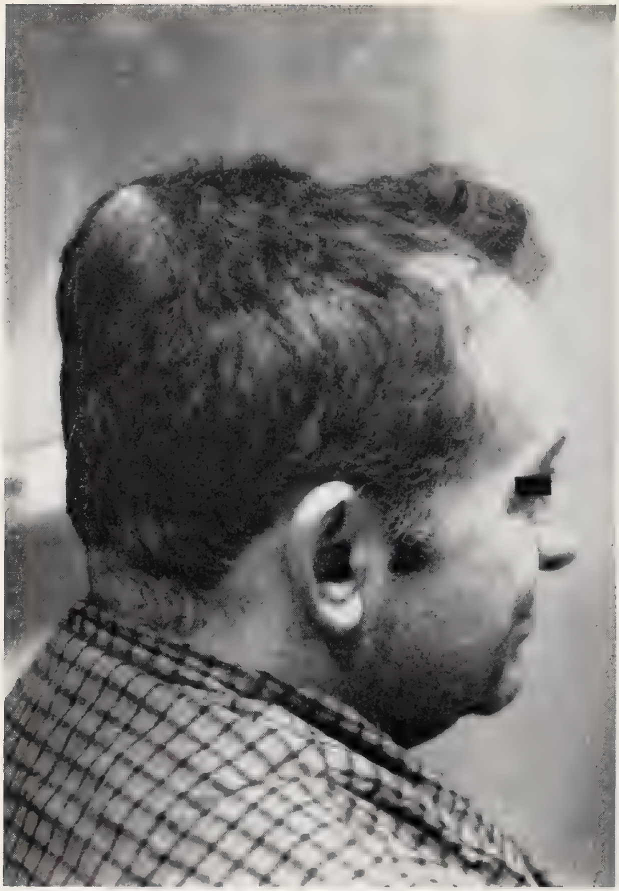

FIG. 1. Case 1. Round prominence on the posterior aspect of the head, angiographically shown to be a meningioma.

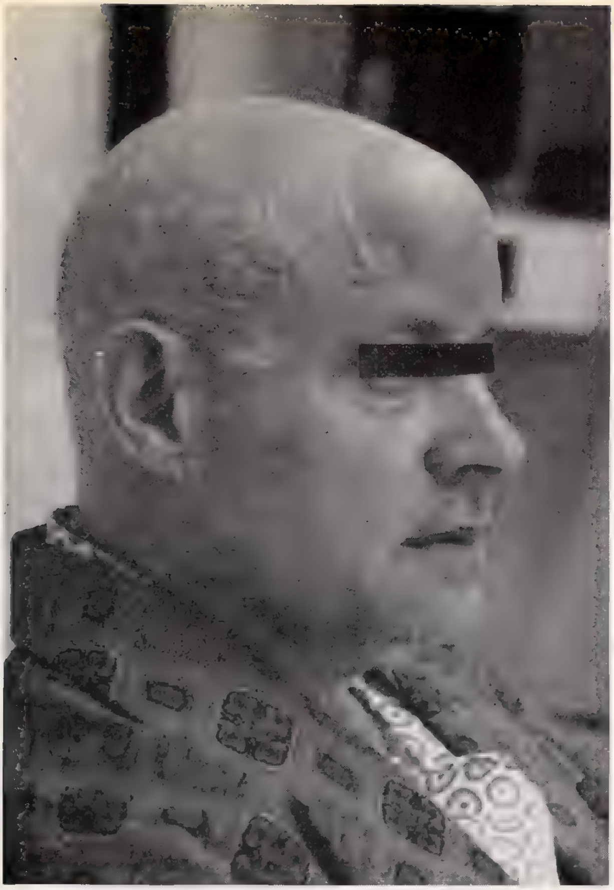
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FIG. 2. Case 2. Large prominence going across the midline of the forehead. Note the tortuous artery leading to the margin.

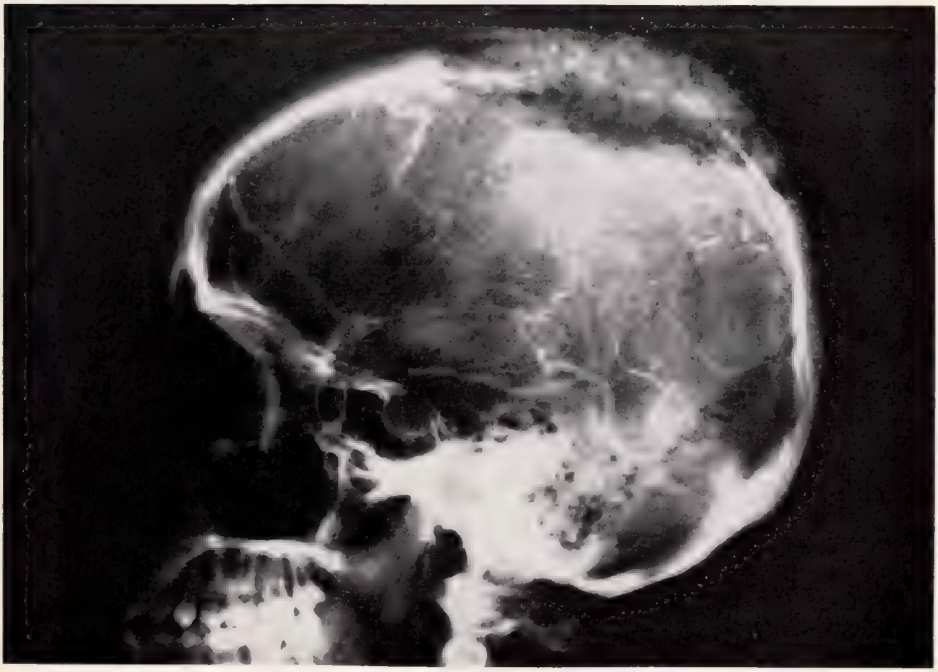

FIG. 3. Case 3. Right lateral view of a cerebral angiogram, early venous phase showing a vascular meningioma involving the superior sagittal sinus.

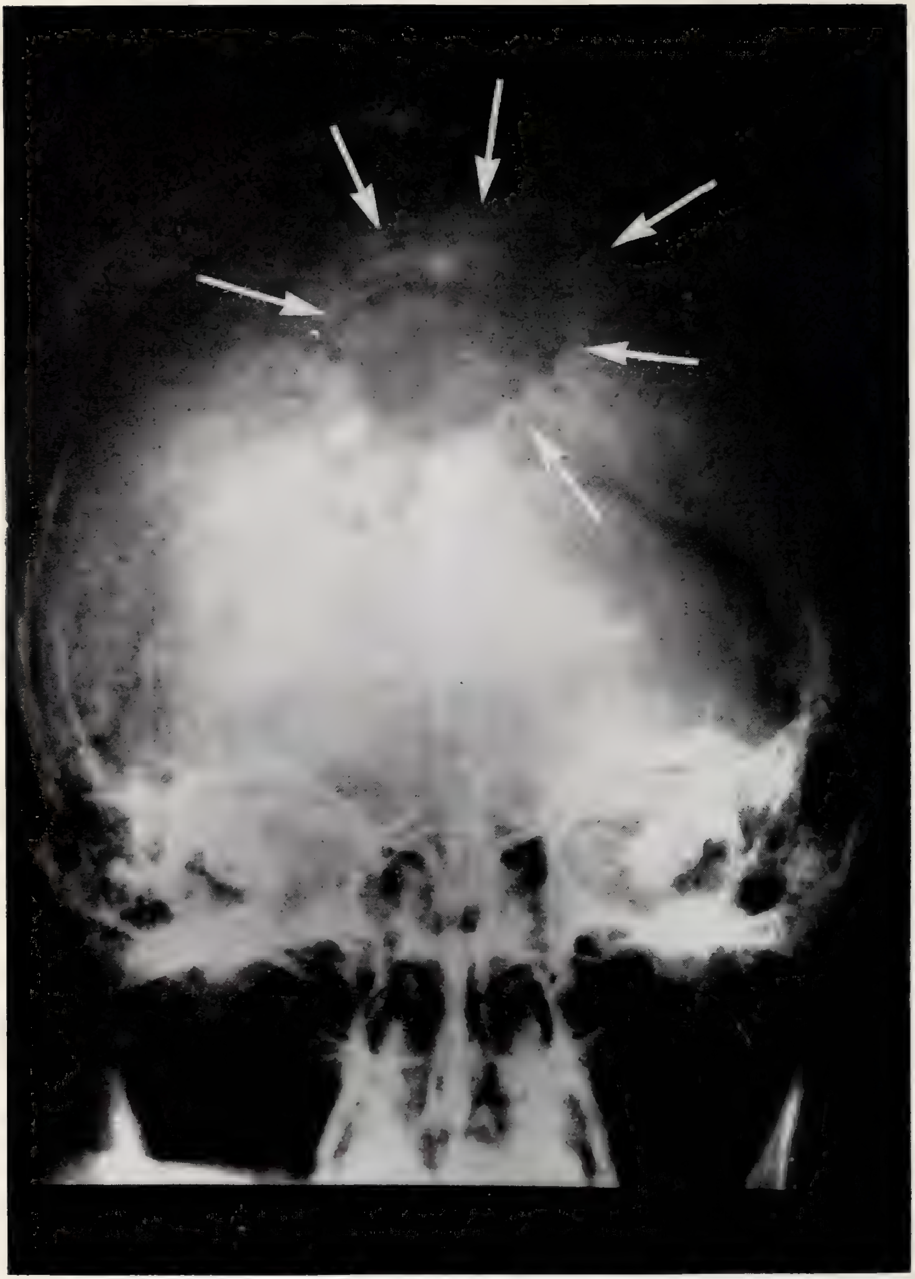

FIG. 4. Case 4. Anterior-posterior skull x-ray. The arrows outline a midline bony defect underlying a protruding meningioma.

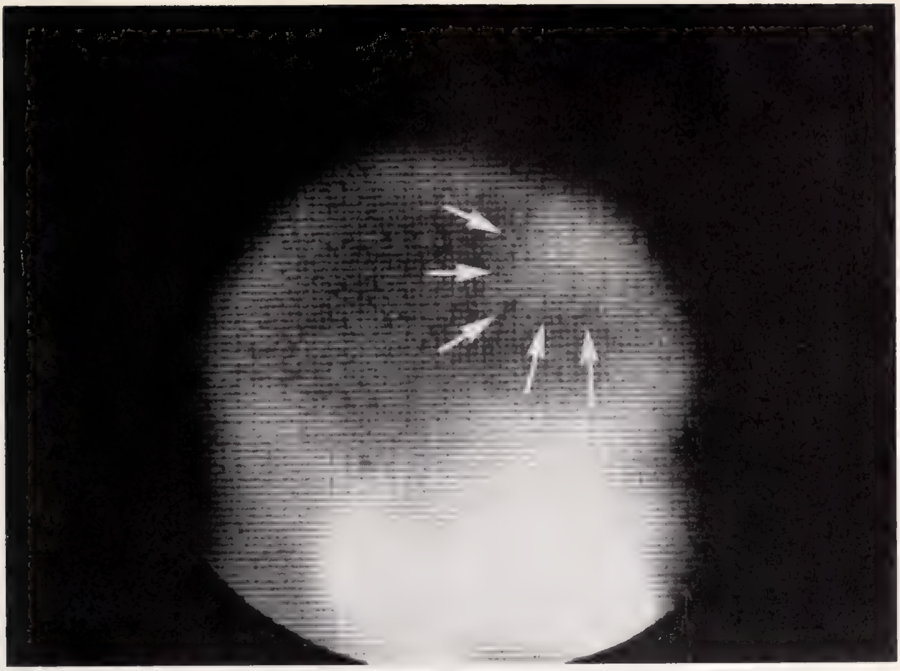

FIG. 5. Lateral view of a Technetium^{99m} brain scan. The arrows outline uptake of the isetope in the frontal area.

complaint that toward the end of November 1971 he had accidentally bumped his head against a steam pipe. He did not lose consciousness. He went to the hospital because of headache and was found to have a swelling of the front part of his head. The headache disappeared after a few days. However, the swelling persisted. The patient insisted that the swelling was not present prior to October 1971. Neurologic examination was negative. There was a large, thick swelling over the bregma in the frontal region, bilaterally. It was thought to be overlying a bony defect in the skull (Fig. 4). Angiography was performed and showed a large meningioma crossing the midline.

Discussion

Meningiomas may grow slowly for many years and attain very large size due to the fact that they tend to displace the brain rather than invade it. Cushing and Eisenhardt (1) give examples of cases where the history could be traced back twenty or thirty years. They most frequently cause neurologic signs without any external evidence of their presence, but occasionally these tumors will invade the calvaria, causing both destructive and productive changes which result in a prominent elevation on the skull. This may occur so slowly that only some minor trauma at or near the site will bring attention to the area.

In dealing with these prominences clinically a routine skull film and brain scan should be done. These tumors often calcify or cause bone destruction, as in our fourth case. Occasionally, when the skull film is not revealing, the brain scan is. These tumors are quite vascular and show up well on both routine and

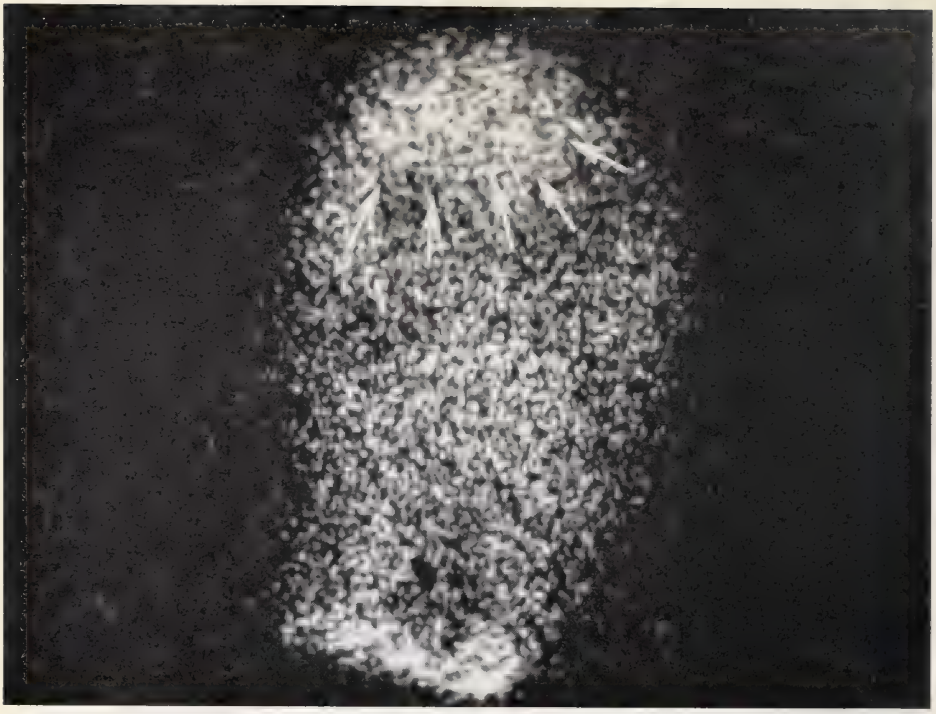

FIG. 6. Dynamic brain flow study using Technetium^{99m} in Case 4. The picture is taken at 10 seconds, and shows increased vascularity on the right and going across the midline. The area is outlined by arrows.

dynamic brain scans (Figs. 5 and 6). In two large series the correlation between brain scans and meningiomas later proven by angiography and surgery has been in the 80 to 90 percent level (3, 4).

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Residual Cerebellar Systems Dysfunction and Peripheral Neuropathy after Diphenylhydantoin Therapy

JOHN O. LUSINS M.D. AND ROBERT JUTKOWITZ M.D.

Abstract

Reversible toxicity during diphenylhydantoin therapy is commonly observed. Persistent toxicity is far less often observed. A case is presented of a young man who was documented during therapy to have unusually high levels of diphenylhydantoin in the serum. He gradually developed signs of cerebellar system dysfunction as well as peripheral neuropathy. This has persisted 22 months after the cessation of diphenylhydantoin. The factors that may result in permanent toxicity are discussed, as well as the mechanism by which the diphenyldantoin may produce this toxicity.

Since the introduction of diphenylhydantoin in 1938 its safety and efficacy have been attested to by its world wide acceptance. A great many patients have been treated, and some of these have had evidence of diphenylhydantoin intoxication (1, 2). This, however, disappears completely with the removal of the drug. A smaller number have been suspect of having sustained more permanent damage (3–8).

We recently observed a young man who we feel may fit into this group. He had been taking diphenylhydantoin for two and a half years and during this time he had unusually high serum levels of diphenylhydantoin. He was admitted with neurologic evidence of cerebellar system dysfunction and with a peripheral neuropathy. Both of these conditions developed during the period of diphenylhydantoin therapy. This cerebellar system dysfunction and neuropathy has persisted for 22 months following cessation of diphenylhydantoin and all other medication.

Case Report

In 1965, H.S., at age of 21, was injured in an automible accident. This resulted in coma for 30 hours and in two weeks of hospitalization. At the time of his discharge, the neurologic, examination of the patient was normal. Three weeks later he began having grand mal seizures on the average of two to three times a week. He had six brief hospitalizations in a two-year period. During that time he underwent three electroencephalograms, all reported as being normal. A pneumoencephalogram was done and reported as normal. On July of 1966 he was started on 300 mg per day of diphenylhydantoin and after three months of therapy gradually started to develop difficulty with gait and slurred speech.

The patient was admitted to the Bronx Veterans Hospital in August of 1967 because of poor seizure control and difficulty with balance. He was noted to be a thin young white man, 23 years old. He appeared to be of average intelligence. He was dysarthric. There was sustained nystagmus on vertical and horizontal gaze. The remainder of the cranial nerves were unremarkable. Finger-to-nose testing showed coarse tremor and past pointing. He had difficulty with balance in sitting position. and could not stand by himself. Heel to knee testing showed bilateral ataxia. He had difficulty with plantar dorsiflexion of both feet. The remainder of the motor system was within normal limits. Sensory testing revealed position

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errors and diminished vibratory sensation in the lower extremities. Ankle jerks were absent. All other reflexes were present. No pathologic reflexes were noted.

On admission the CBC—HTC, urinalysis, and serum electrolytes were normal. Lumbar puncture showed an opening pressure of 120 mm of water; protein, 31; and glucose, 54. Electromyogram showed right posterior tibial conduction velocity of 31 meters/sec; the left, 30 meters/sec. Electroencephalogram showed basic rhythm to be alpha 8–9 cps, with occasional slowing into the 5–7 cps range, bilaterally and diffusely.

In the hospital stay during the first year the patient had frequent episodes of loss of consciousness. These occurred as often as three times in a 48 hour period. These were associated with generalized convulsive activity, and were followed by a period of unresponsiveness and confusion. There was no aura and there was never noted a laterality or focality to these convulsive episodes. Control was attempted with diphenylhydantoin and primidone. Toward the end of 1968 these seizures had decreased to one every two to three weeks. They ceased completely by the middle of 1969. The patient's dosage of diphenylhydantoin and primidone was concomitantly decreased. These dosages are charted on Figure 1. The serum levels of diphenylhydantoin were also monitored and are charted on Figure 2. Since March of 1970 he has been off anticonvulsants completely.

On the most recent examination on December of 1971 the patient continued to have findings presumably associated with diphenylhydantoin toxicity. He could not stand without support because of poor balance. He had titubation of the head at rest, and this increased with voluntary movement. He had coarse sustained nystagmus present in both vertical and horizontal gaze. His speech was dysarthric. Finger-to-nose testing and heel-to-knee testing revealed movements which were grossly ataxic. The strength in doors inflexion of the feet was decreased and ankle jerks were bilaterally absent. Position and vibratory sense was decreased in both lower extremities. The last EEG was normal. The conduction velocities in lower extremities were reduced as in the previous EMG. A right brachial angiogram performed in May of 1971 showed normal ventricular size and no abnormalities of the vasculature.

Discussion

Why some individuals develop permanent dysfunction from the drug and others do not is not understood. Certain factors should be considered. The duration of exposure to high blood levels of diphenylhydantoin appears to be

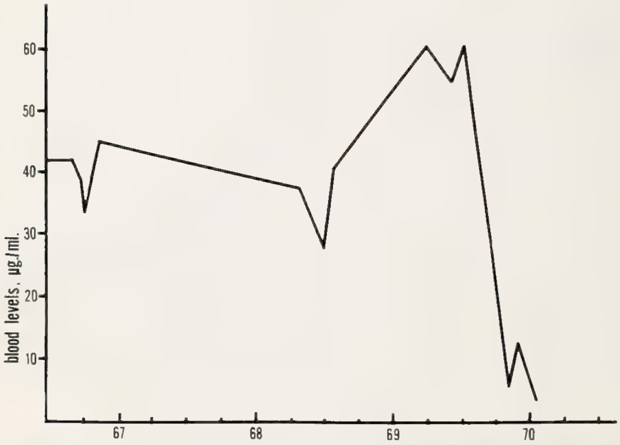

FIG. 1. Blood levels of diphenylhydantoin during the period that it was being administered.

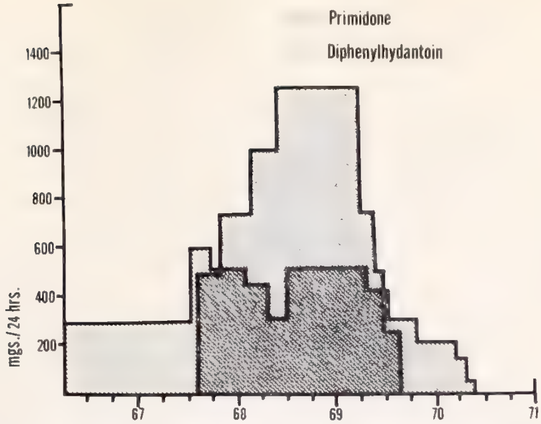

FIG. 2. Daily dosage of diphenylhydantoin and primedone.

significant. Animal experiments have shown that the greatest cellular change has been in those animals who were on the highest doses for the longest time (8). Kutt et al (15) have reported that in humans toxicity occurs at a serum level of 20 μg/ml and becomes fully manifest at levels of 40 μg/ml. Our patient's blood levels were frequently at the 50 μg/ml level for prolonged periods of time.

There may also be a difference in a degree of susceptibility. Kokege et al (8) reported that there was a significant difference in the cellular damage in animals who were similarly maintained, and who had similar blood levels of diphenylhydantoin.

Also it is not certain why different blood levels are attained by individuals taking the same dosage of diphenylhydantoin. Kutt (16) feels that the variability is due to different rates of hydroxylation of diphenylhydantoin by the liver. He suggests that this may be due to a genetic predisposition, and describes a family who could not handle less than average doses of diphenylhydantoin. Their blood levels rapidly rose to above 80 μg/ml.

It may be that other drugs play a role in maintaining elevated levels of diphenylhydantoin in the serum. Kutt (17) has shown that isoniazid, PAS, and cycloserine inhibit diphenylhydantoin metabolism. He likewise has shown that phenobarbital alters diphenylhydantoin serum levels (18), increasing these levels in some individuals and decreasing these serum levels in others. This occurred in no predictable manner. Since primidone is structurally closely related to phenobarbital, it may have similar action. Our patient was receiving primidone for a major portion of the time that high diphenylhydantoin levels were reported.

The mechanism of diphenylhydantoin damage is not certain. Animal experiments by Utterbacher (5), Dam (9), and Kokege et al (8) showed that animals kept on high doses of diphenylhydantoin have changes primarily in the cerebellum and most severely in the Purkinje cells. These changes consist of swelling, shrinkage and vacuolation, and then complete disappearance of the neuronal component of the cerebellum. Similar changes have been described by Snider and Del Carro (12) and Hoffman (4) in the cerebellum of patients dying while on high doses of diphenylhydantoin. Dom (11), after repeating some of his earlier animal experiments recently, has stated that the changes previously reported are not significant and can be explained as fixation artifact. Less easily explained changes have been reported by Snider and Del Carro (10) with the use of the electron microscope. They claim that one of the earliest changes noted in animals kept on high doses of diphenylhydantoin has been the presence of dandritic sproutings from the Purkinje cells prior to their developing the changes later seen by light microscopy.

As far as we can determine no one has attempted to duplicate peripheral neuropathy with diphenylhydantoin in animal experiments. Birket-Smith and Krogh (13) have show in 24 patients that diphenhylhydantoin in high doses causes a significant degree of lowering of nerve conduction velocity. With the reduction of blood levels of diphenylhydantoin the conduction velocity returns to normal, indicating that the effect of short duration of elevated diphenylhydantoin levels on the conduction velocity must be a pharmacologic one. Lowelace and Horowitz (14) in their study of patients on long-term diphenylhydantoin therapy found 20 patients with lower extremity areflexia. Nineteen of the 20 patients had been on diphenylhydantoin for at least 20 years, and 18 had evidence of significant toxicity somewhere in their course. Over half had daily dosages of 400 mgs. They also found that in eight patients who were on diphenylhydantoin and who did not have reflex changes there was conduction velocity slowing of the posterior tibial nerves that was statistically significant in comparison with a group of normal subjects not receiving diphenylhydantoin. They did not decrease the dosage of the areflexic group to ascertain if the conduction velocity would improve as it had in the short-term group of Birket-Smith and Krogh.

Summary

We have described the case of the young patient who has evidence of cerebellar system dysfunction and peripheral neuropathy 22 months after the cessation of diphenylhydantoin therapy. During the time that he was receiving diphenylhydantoin he was noted to have remarkable elevated serum levels of diphenylhydantoin. It was considered that a low rate of hydroxylation or interaction with other drugs may have had a role to play in the production of persistently high srum levels.

Most clinicians are aware of the signs of cerebellar systems toxicity with diphenylhydantoin, however, they should also be aware that the peripheral nerves may likewise be involved. This involvement may first appear only as a change in the conduction velocity. Further investigation has to be done to determine if individuals who have been on long-standing diphenylhydantoin therapy and have peripheral toxicity improve if the serum levels are significantly decreased.

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